MARCH 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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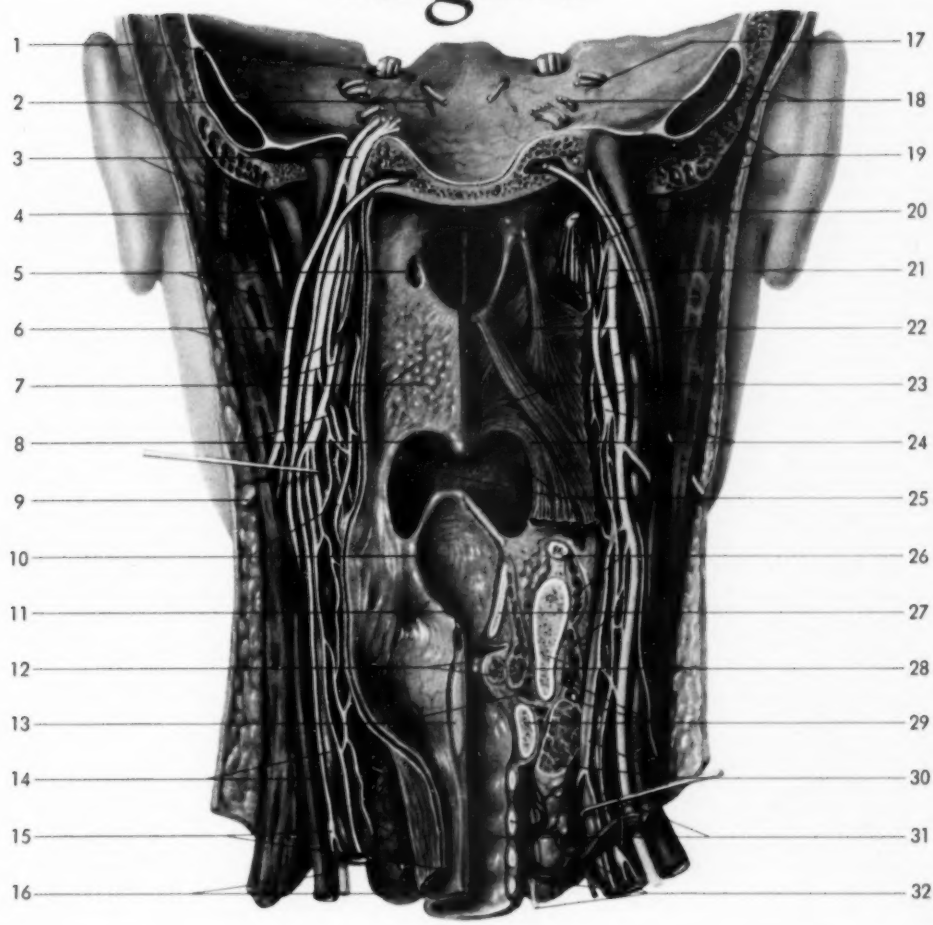

1 Trigeminal nerve
2 Splenius capitis muscle; abducens nerve
3 Longissimus capitis muscle; intracranial ganglion of vagus nerve
4 Occipital artery; styloid process
5 Digastric muscle; pharyngeal opening of auditory tube
6 Sternocleidomastoid muscle; hypoglossal nerve
7 Internal carotid artery and nerve; mucous glands of pharynx
8 Superior laryngeal nerve; palatine uvula
9 Accessory nerve
10 Pharyngeal branch of vagus nerve; epiglottis
11 Arytenoid muscle; ventricular fold
12 Vocal fold; vocalis muscle
13 Cricoid cartilage; lateral cricoarytenoid muscle
14 Sympathetic trunk; common carotid artery
15 Middle cervical ganglion; esophagus
16 Internal jugular vein; thyroid gland
17 Facial and acoustic nerves
18 Glossopharyngeal nerve; sigmoid portion of transverse sinus
19 Mastoid cells; internal jugular vein
20 Otic ganglion; ascending pharyngeal artery
21 Salpingopharyngeus muscle; nodose ganglion
22 Levatorveli palatini muscle; vagus nerve
23 Pharyngopalatinus muscle; superior laryngeal nerve
24 Stylopharyngeus muscle; superior cervical ganglion
25 Palatine tonsils
26 Greater cornu of hyoid bone; thyrohyoid muscle
27 Quadrangular membrane; sternothyroid muscle
28 Thyroarytenoid muscle; thyroid cartilage
29 Cricoid cartilage; superior thyroid artery and vein
30 Thyroid gland (cut); superior cardiac nerve
31 Trachea and tracheal cartilage; sympathetic trunk
32 Inferior thyroid artery and vein; recurrent laryngeal nerve

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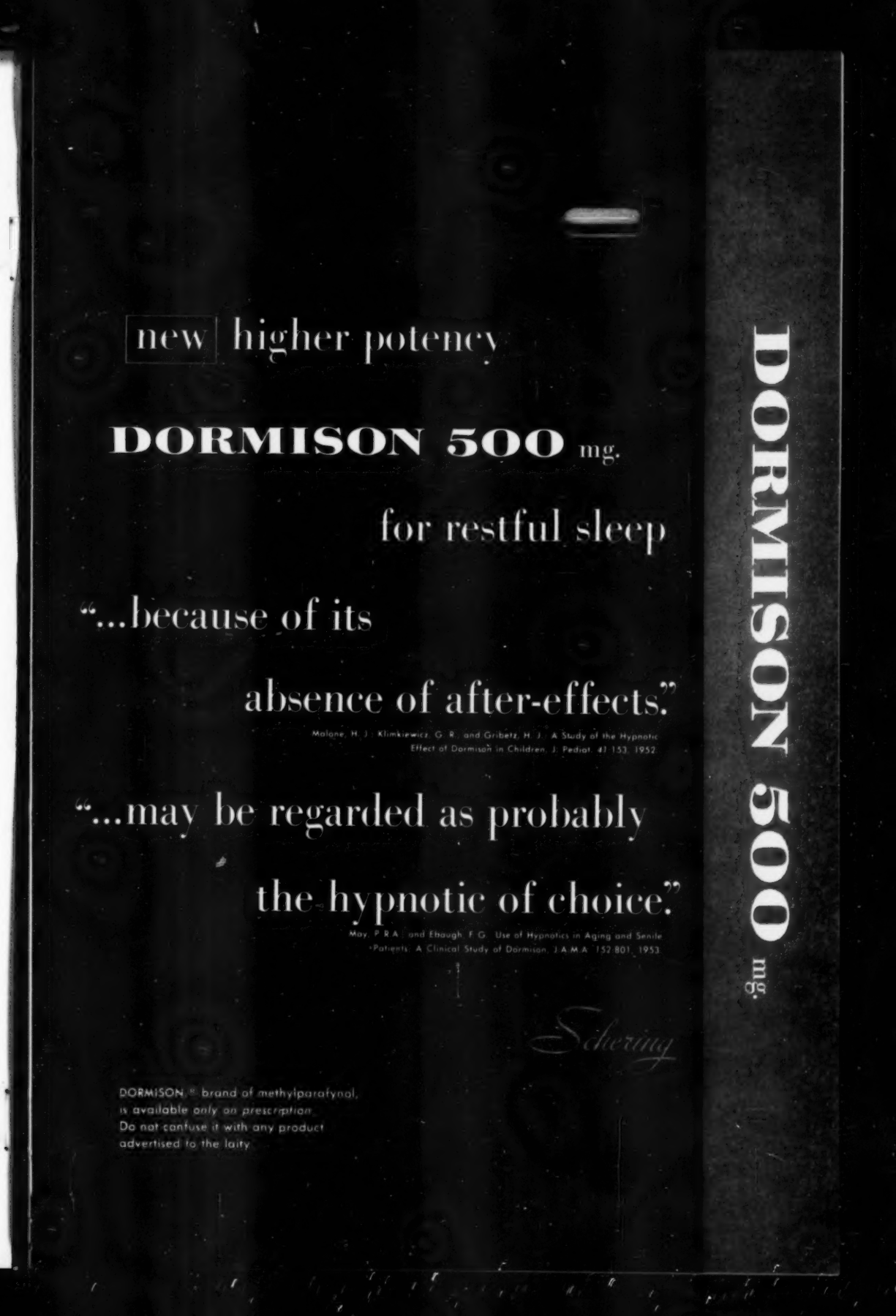
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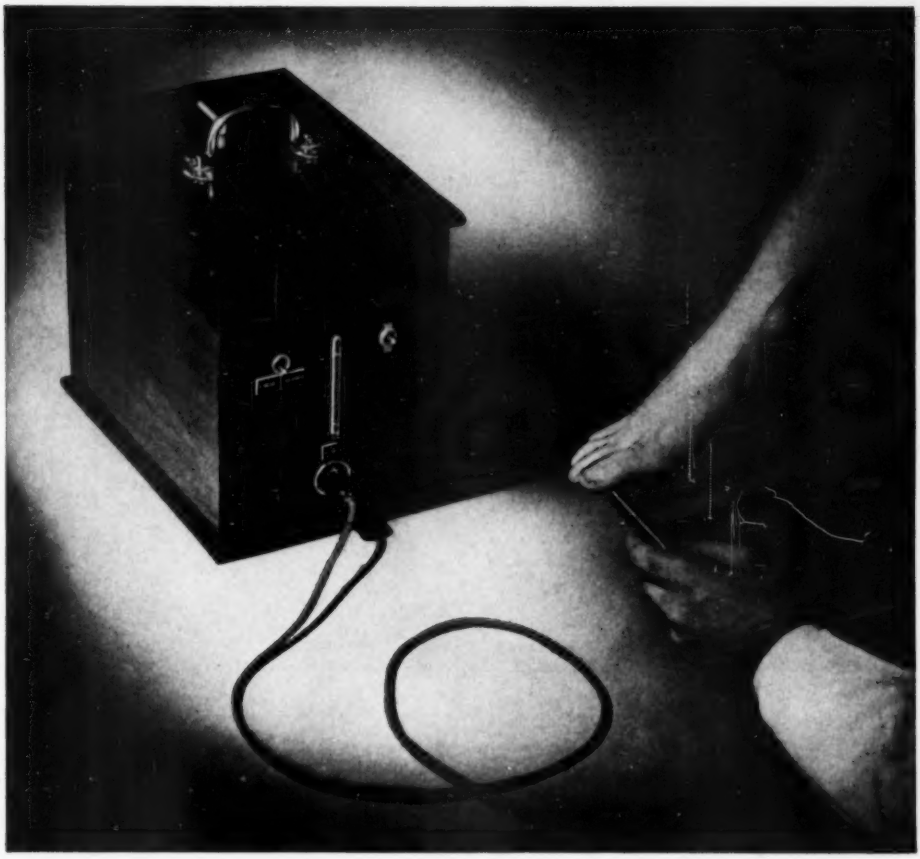

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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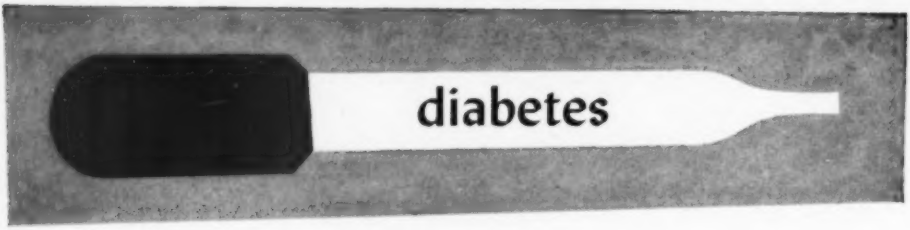

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1. Blotner, H., and Marble, A.: New England J. Med. *245*:567 (Oct. 11) 1951.
2. Steine, L.: GP *8*:45 (July) 1953.

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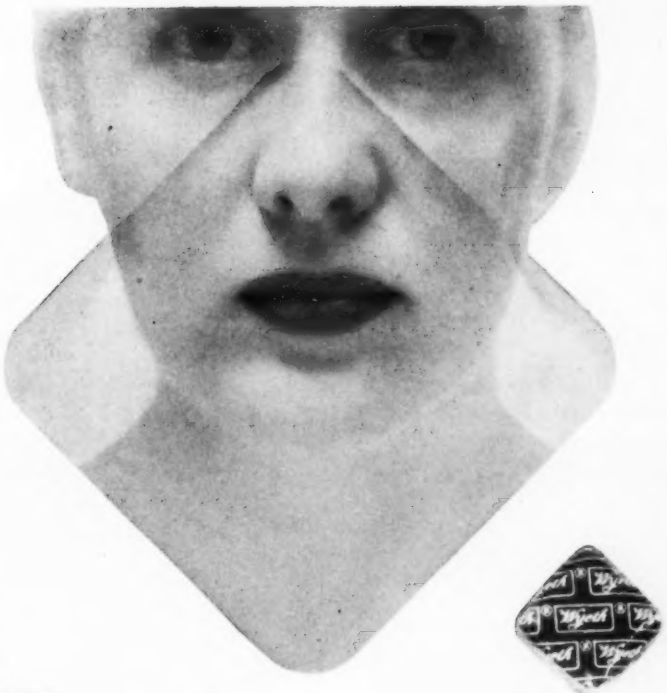

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1. Frank, P.F., Wilcox, C., and Finland, M.: In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics, J. Lab. & Clin. Med. *35*:188 and 805, 1950.
2. Jawetz, E. and Coleman, V.R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B), J. Lab. & Clin. Med. *34*:751, 1949.
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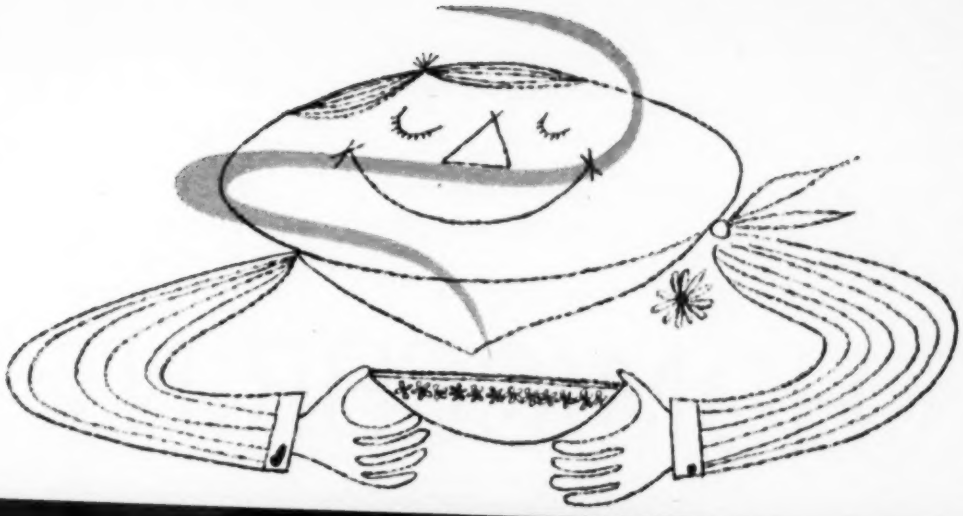

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BULLETIN OF
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OF MEDICINE

VOL. 30, NO. 3 MARCH 1954

ANEMIAS IN INFANCY AND CHILDHOOD: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS*

CARL H. SMITH

Associate Professor of Clinical Pediatrics, Cornell University Medical College, New York, N. Y.

RECENT comprehensive surveys and studies of the manifold aspects of normal and disturbed hematopoiesis have unravelled many of the fundamental problems associated with the anemias of infancy and childhood. Pediatrics has not alone been the beneficiary of these advances, but has made its own contributions notably in relation to erythroblastosis and megaloblastic anemia of infancy by discoveries of major importance and wide application. The combined effect of expanding hematologic knowledge derived from diverse fields permits a better understanding of pathogenetic mechanisms, a more accurate appraisal of diagnostic data, a greater selectivity of antianemia agents and the characterization of new entities. The rapid development of pediatric hematology can be strikingly illustrated by recalling the fate of von Jaksch's anemia. This syndrome which dominated the section of anemia in pediatric textbooks of thirty years ago, receives scant mention or is entirely omitted from pres-

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, October 22, 1953. From the Department of Pediatrics, The New York Hospital-Cornell Medical Center. The data included in this paper are based on studies supported in part by a research grant (A-227) from The National Institute of Arthritis and Metabolic Diseases of The National Institute of Health, Public Health Service; The Children's Blood Foundation, Inc.; the United Hospital Fund and Mead Johnson & Co.

TABLE I—FACTORS INFLUENCING THE BLOOD PICTURE IN THE NEONATAL PERIOD AND EARLY INFANCY

1. The results of maternal isoimmunization by fetal blood factors.
2. Fortuitous leaks of fetal blood into the maternal circulation as complications of delivery.
3. Fluctuations in blood volume as related to early or late tying of the cord.
4. Substitution of adult for fetal hemoglobin.
5. The aregenerative phase of erythropoiesis which characterizes the early months of life.
6. The possibility that a blood dyscrasia may represent a congenital or developmental defect.
7. The effects of prematurity.
8. The effects of rapid body growth.
9. The greater potential capacity of the hematopoietic system to react excessively.
10. Inadequate fetal stores of iron from maternal deficiency of this mineral.

ent day publications. The dismemberment of this heterogeneous group of blood disorders now replaced by more soundly based conditions, was initiated by Cooley when he separated from it the anemia that now bears his name. Little remains of the original designation except for infrequently reported cases still difficult to classify but meeting its ill-defined criteria.

It is obvious that it would be impossible to compress within the limits of this presentation all the subjects that properly belong to it. It is my purpose, therefore, to provide a basis of orientation by which the diagnostic features of the common anemias observed in the care of infants and children may be detected and rational therapy instituted. It is hoped also to emphasize that these objectives may be achieved by the judicious application of readily available information and the employment of a few simple laboratory procedures. In the course of this discussion several closely related aspects of iron metabolism, transfusions and splenectomy in which my associates and I have been interested for several years will be dealt with at greater length.

In this connection, I should like to state that for the development of the various concepts and the data upon which they are based, I am indebted to all of my associates, especially to Dr. Irving Schulman, who has actively collaborated in these studies.

TABLE II—ANEMIAS OF INFANCY AND CHILDHOOD

Diagnosis: Orientation and Methods

1. History and physical examination
2. Basic blood studies: complete blood count, reticulocytes and interpretation of blood smear
3. Comparison with normal range of blood values for each age period
4. Etiological classification
   - A. Blood loss
   - B. Excessive blood destruction and hemolysis: extra- and intra-corpuscular origin
   - C. Bone marrow depression or infiltration
   - D. Deficiency of building materials for hemoglobin or red cell formation
5. Reference to age periods of most frequent occurrence
6. Bone marrow examination
7. Roentgenographic examination
8. Study of hereditary factors
9. Therapeutic response to iron, folic acid, citrovorum factor, B_{12}, liver, transfusion
10. Specialized laboratory procedures:

A. Essential	Stool guaiac test
	Serum bilirubin
	Blood urea nitrogen
	Coombs' test
	Red cell fragility
B. Helpful	Gastric acidity
	Stool urobilin
	Serum iron and latent iron-binding capacity
	Bone marrow iron
	Electrophoresis for sickle cell and other types of hemoglobin

FACTORS INFLUENCING THE BLOOD PICTURE IN THE NEONATAL PERIOD AND EARLY INFANCY

As a background for appraising a specific blood picture, it should be remembered that the diagnostic features of the anemias of infancy and childhood as differentiated from those of older age groups, are influenced by certain inherent physiologic and anatomic changes which originate within and outside of the hematopoietic system. These influences operate with diminishing force from birth to adolescence although many of these have originated in prenatal life. In no area is there a

greater need for being cognizant of the operation of underlying mechanisms than in the neonatal period. In the newborn and young infant the blood picture reflects a response to such varied forces as are recorded in Table I.

Orientation and Diagnostic Methods

In investigating a suspected anemia, it will be found that diagnosis can be facilitated by the appraisal of data derived from a variety of sources such as those listed in Table II. The large number of items included in this schedule illustrates the wide scope of available information and technical procedures upon which it is based. However, an insight into the nature of the anemia usually confronting the practitioner requires that relatively few of these topics need be probed. Under ordinary circumstances a thorough history, physical examination and basic blood studies with concomitant reference to the type of working classification noted in this table will not alone suffice to determine the type of anemia but the treatment which is indicated.

Appropriate therapy is inseparable from knowledge of etiology, diagnosis and classification and some concept of pathogenesis. With the application of these readily available exploratory measures, it is possible to separate a primary derangement of hematopoiesis from a secondary anemia which may be symptomatic of some other type of blood dyscrasia. Interrogation along broad lines of causation should be directed towards the onset of pallor, of purpura, of crises associated with pallor or jaundice, the loss of blood from the bowel, infection, prematurity, the use of drugs known to affect hematopoiesis, hematemesis, exposure to animal parasites, renal disease, rate of weight gain, overfeeding of milk and refusal to eat solid foods, race, nationality and familial incidence. Physical examination should include such diverse features as pallor, jaundice, skin pigmentation, enlargement of the lymph nodes and spleen, petechiae, the character of the nails, cardiac enlargement, and facial configuration.

When infection which is responsible for the major number of anemias in young children is excluded as an etiologic factor, the remaining blood dyscrasias can be grouped for orientation according to age periods of their most frequent incidence: newborn, infancy, and childhood. The diagnostic features of erythroblastosis and of hemorrhagic disease of the newborn are apparent at birth or shortly thereafter. Pure

red-cell (chronic congenital aregenerative) anemia, the anemia of prematurity and iron deficiency anemia are detected in the earlier months of infancy, megaloblastic anemia of infancy between two and eighteen months of age and aplastic and hypoplastic anemia during any period of childhood.

It must also be emphasized that the onset of anemia first recognized in older infants and children precedes by a variable period, the time when the distinguishing features of the condition are fully established and unequivocal. This applies particularly to congenital spherocytic anemia, sickle cell anemia and Mediterranean anemia which develop insidiously so that diagnosis is often difficult before specific criteria are fully established. Assiduous examination, however, will often disclose their presence as far back as the neonatal period when they are to be suspected on the basis of familial incidence. Of the three syndromes, diagnostic cells are least likely to be found in the blood of the newborn in sickle cell anemia. Sickling in affected infants may not appear until three to four months of age. Watson[1] has postulated that since this period is characterized by the persistence of fetal hemoglobin which is unable to sickle, this phenomenon could not be expected to appear until it had been replaced by sufficient sickle cell hemoglobin.

Normal Blood Values in Infancy and Childhood

It is important to point out that because of developmental changes, anemias in infancy and childhood must of necessity be interpreted in the light of the contemporary hematologic framework within which they are encountered. In Table III is summarized the range of normal values for the respective age periods which serves as a basis for evaluating a hematologic abnormality. There are several features that are worthy of mention in connection with erythroblastosis.

In the first place, the hemoglobin values as stated are usually based on peripheral blood samples. Mollison and Cutbush[2] have emphasized, however, that in suspected cases of erythroblastosis an exception must be made and it is obligatory to measure the hemoglobin value on cord blood. The latter serves as a more accurate index of the blood status and guide to treatment than the higher values of venous blood and even more elevated reading by skin puncture. These discrepancies are due to variations introduced by the delayed tying of the umbilical cord which can account for an increment of 100 cc. of blood out of a total of 125

TABLE III—ANEMIAS OF INFANCY AND CHILDHOOD
SIGNIFICANT NORMAL VALUES

Hemoglobin	1st day	20 Gm. (18-22 Gm.)
	2 weeks	17 Gm.
	1st 2 years	11 Gm. (10-12.5 Gm.)
	3-5 years	12.5-13 Gm.
	5-10 years	13-13.5 Gm.
	10 years to puberty	14.5 Gm.
Red blood cells	1st day	5,500,000 (5-6 million)
	2nd week	5,000,000
	Older infant and child	4,000,000 per cu. mm. lower limit of normal
Nucleated red cells	Average at birth ranges from 3-10 per 100 white cells.	
Reticulocytes	0.5 to 1.5 per cent (Below 0.5 per cent in aplastic and hypoplastic anemia. Increased in hemolytic anemias; in deficiency anemia rise from low to high levels with treatment).	
Volume of packed red cells	Infants and children	36 per cent is lower limit of normal
	Older age groups	40 per cent minimum
Serum bilirubin	Newborn full term infants 2-8 mg. per cent Newborn premature infants 1-15 mg. per cent } Rise during 1st week Normal infants and children under 1 mg. per cent (Hemolytic anemias—elevated total bilirubin predominantly indirect fraction).	
Fragility test	Normal range 0.425 to 0.325 per cent sodium chloride. (Increased fragility in congenital hemolytic jaundice and in some cases of acute hemolytic anemia. Decreased fragility in sickle cell anemia, Mediterranean anemia and in iron deficiency anemia).	

to 150 cc. present in the placenta. The rapid shift in the plasma soon after birth is reflected in higher concentrations in the peripheral blood as compared with cord blood. Thus, Mollison and Cutbush[2] cite an infant with a cord blood hemoglobin of 12.8 grams per cent, in whom venous and capillary blood samples taken a few hours after birth revealed hemoglobin levels of 15.4 and 18 grams respectively. It is possible, therefore, for cord blood to show anemic levels indicating the need for treatment, while the peripheral hemoglobin values are normal or elevated.

The cord blood hemoglobin concentration of 16.6 grams (16.55 ± 1.5) noted by these authors in healthy infants compares with values in our laboratory of 16.4 (16.4 ± 1.09). Although strict interpretation would restrict replacement therapy to values below the lower limits of normal (approximately 13.6 gm.), experience has shown that the individual case cannot be sharply defined, but has to be assessed in terms of a large number of factors including previous history, clinical condition of the patient, blood and related serological values.

Crosby and Akeroyd[3] have demonstrated the remarkable capacity of the bone marrow to respond to the demands of abnormal hemolysis by maximum erythropoietic efforts so as to maintain a normal volume of red cells in the circulation. For example in the crises of sickle cell anemia, the hemoglobin level may remain unchanged but the reticulocytes are elevated to indicate accelerated bone marrow activity to compensate for the increase in hemolysis. Similarly, in the erythroblastotic infant augmented reticulocyte values with a normal red cell count on the first day of life may indicate increased red cell turnover and the need for close watch in succeeding days for the development of anemia and jaundice.[4]

The estimation of serum bilirubin concentration has assumed increased significance as an index of the severity of blood destruction especially in erythroblastosis in which it also serves as a guide in management. The designation of a range of normal values (as given by Hsia, Allen, Diamond and Gellis[5]) serves to differentiate the changes in healthy infants who develop "physiological jaundice" from those attained in erythroblastosis. The rapid rise in bilirubin concentrations and the earlier appearance of clinical jaundice noted within the first day of life in erythroblastosis contrasts with its later development in normal infants. Hsia and his co-workers[5] state that levels exceeding 10 mg. per cent in the first twenty-four hours after birth are commonly observed in erythroblastosis but rarely in other infants, and that a level of 5 mg. per cent in the cord blood is highly suggestive of erythroblastosis. The slower development of increased bilirubinemia in the full-term infant which is more prolonged and reaches higher levels in the premature infant has been attributed to hepatic immaturity.

An additional feature in the management of erythroblastosis pertains to the usefulness of determining the fetal hemoglobin percentage before and after exchange transfusions. In a small series of cases, we have found

TABLE IVa—ANEMIAS OF EARLY INFANCY

Type of Anemia	*Diagnostic features of the blood smear*
Erythroblastosis fetalis	Hyperchromic macrocytes, nucleated red blood cells
Hemorrhagic anemia	Acute blood loss: normochromic and normocytic red blood cells
	Chronic blood loss: hypochromic microcytes
Iron deficiency anemia	Hypochromic microcytes, marked central pallor of red blood cells, poikilocytes
Anemia of Prematurity	Early: normocytic and normochromic red blood cells
	Later: hypochromic microcytes
Megaloblastic anemia of infancy	Very large macrocytes, microcytes, occasional nucleated red blood cells, abnormal neutrophiles

that the comparison of these values serves as an approximate index of the extent of the exchange.

DIAGNOSTIC FEATURES OF THE BLOOD SMEAR

Of all laboratory procedures, the most important for its diagnostic value, yet the simplest, is the examination of the blood smear. While corroborative evidence from auxiliary sources may be required to establish a final diagnosis, the stained blood film constitutes a visual representation of the effect on morphology of the factors involved in the pathogenesis of a specific anemia. In describing the changes in the red blood cells, it should be pointed out that except for sickle cells, spherocytes and leptocytes—the large, pale, extremely thin, ridged erythrocytes with irregularly distributed hemoglobin observed in advanced Mediterranean anemia, there are no specific red cells that are indicative of a particular disorder. Even the small, deeply stained spherocytes which characterize congenital spherocytic anemia, may also be observed in greater or less degree in other conditions associated with hemolysis such as acquired hemolytic anemia, erythroblastosis due to sensitization by the A-B agglutinogens and in leukemia. Target cells, oval cells, hypochromic macrocytes and basophilic stippling and hypochromic

TABLE IVb—ANEMIAS OF LATER INFANCY AND CHILDHOOD

Type of Anemia	*Diagnostic features of the blood smear*
Anemia of infections	Normocytic and normochromic, occasionally microcytic and hypochromic red blood cells; with iron deficiency hypochromic microcytes predominate.
Aplastic, hypoplastic and aregenerative (pure red-cell) anemia	Normochromic and normocytic red blood cells.
Acquired hemolytic anemia	Moderate spherocytosis and reticulocytosis.
Congenital spherocytic anemia	Large number of spherocytes and reticulocytes.
Sickle cell anemia	Sickle cells, target and oval cells, hypochromic macrocytes.
Mediterranean anemia Severe type	Very large thin hypochromic macrocytes, nucleated red blood cells, marked poikilocytosis and anisocytosis.
Mild type or trait	Hypochromic macrocytes, microcytes, basophilic stippling, polycythemia, target and oval cells.

microcytes appear in varying percentage in certain stages of many anemias and therefore cannot be regarded as distinguishing features of a single disease. They are of diagnostic value only when they are considered in conjunction with pertinent information from other sources.

The hematic observations for each disorder recorded in Table IV, serve also as a review of the anemias commonly occurring in infancy and childhood. The hypoplastic-aplastic group of anemias reveals overlapping, but for the purposes of definition they can be placed in three general categories. Pure red-cell anemia[6] is a chronic aregenerative anemia, in which the failure of the bone marrow is confined to erythropoiesis without simultaneous depression of the granulocytes, platelets and their precursors. Hypoplastic anemia, with which pure red-cell anemia has heretofore been grouped, currently includes assorted conditions marked by impairment of red cell formation with varying degrees of involvement of granulocytes and platelets. In aplastic anemia, on the other hand, the three principal cellular elements in the bone marrow are depressed resulting in a pancytopenia.

In the classification of constitutionally defective bone marrows may

be included examples of the "Fanconi syndrome." This condition includes the rare association of aplastic anemia with a number of congenital abnormalities, chiefly pigmentation of the skin, testicular hypoplasia and skeletal abnormalities, although, other less common defects have been observed. Originally reported by Fanconi as occurring in three siblings, sporadic as well as familial cases have since been reported.

Hereditary Aspects in Diagnosis: Sub-Types of Mediterranean Anemia (Thalassemia) and of Sickle Cell Anemia. Careful examination of the exceptions to the genetic pattern in severe Mediterranean anemia and in sickle cell anemia, namely, that in every family with a severely affected child both parents show recognizable blood changes, led to the discovery of several sub-types of these diseases. In one type the patient receives the gene for sickling from one parent and the gene for Mediterranean anemia from the other.[7] The simultaneous presence of both factors results in an anemia of variable intensity, moderate splenomegaly and peripheral blood findings of both diseases. In another type[8,9] are individuals who reveal evidences of chronic hemolytic anemia ranging in severity between the sickle cell trait and sickle cell anemia who inherit the gene for sickling from one parent and the gene responsible for an abnormal hemoglobin designated as C from the other. In the fixed smear the significant feature of sickle cell-hemoglobin C disease is the presence of numerous target cells with an absence of sickle cells, although these can be detected in sealed moist preparations. Individuals bearing the trait for hemoglobin C only, are asymptomatic and reveal numerous target cells as the only consistent blood abnormality. The detection and quantitative relationship of the sickling and C hemoglobins are electrophoretically determined.

Nonhemolytic Anemia of the Newborn: This list of blood disorders may also be supplemented by a small group of cases which have recently been reported[10] as "nonhemolytic anemia of the newborn." This syndrome was designated to include those premature and full-term infants who either are anemic at birth or within the first few days of life show a deficiency of red cells and hemoglobin, without jaundice and erythroblastemia. The factors of incompatibility of blood groups, overt hemorrhage, hemolysis and infection are not operative and the outlook based on a limited experience has been favorable. The designation as "nonhemolytic anemia of the newborn" emphasizes its differentiation from erythroblastosis and probably coincides with selected cases of anemia of the

TABLE V—THERAPY OF THE COMMON ANEMIAS OF INFANCY AND CHILDHOOD

Iron	Iron deficiency anemia, anemia of prematurity, chronic blood loss
Folic acid (Citrovorum factor—Folinic acid) Liver Ascorbic acid B_{12}	Megaloblastic anemia of infancy
Transfusion	Erythroblastosis, non-hemolytic anemia of the newborn, anemia due to hemorrhage and infection, aplastic, hypoplastic and pure red-cell (chronic congenital aregenerative) anemias.
Splenectomy	Spherocytic anemia Mediterranean anemia? Sickle cell anemia? Aplastic, hypoplastic and pure red-cell anemias?
ACTH and cortisone	Acquired hemolytic anemia Hypoplastic and pure red-cell anemias? Crises of sickle cell anemia?

newborn reported prior to the discovery of the Rh factor. It may possibly represent the aregenerative phase of erythropoiesis normally occurring in the early months of life with a premature onset in the fetus. While the precise mechanism of its pathogenesis is unknown, it is important in differentiating this group to eliminate the element of occult or frank hemorrhage from the fetal surface of the placenta which Wiener[11] has stressed as a cause of neonatal anemia. Further experience is required to determine whether undiagnosed sequestration of blood into tissues contributes to this syndrome.

PRINCIPLES OF TREATMENT

The information gathered thus far has provided a sufficiently firm foundation with respect to pathogenesis to warrant a consideration of therapy. In Table V are outlined the available agents in current use, designated to correct an underlying deficiency or in ameliorating the disorder by accessory means when direct remedies are not available.

The constant emphasis on the use of specific rather than indiscriminate mixtures of antianemic substances, as recently expressed by Wintrobe,[12] applies with equal force to the present age group. Iron salts given by mouth preferably in the ferrous forms without the aid of supplementary minerals or vitamins still constitute the most effective treatment of iron-deficiency anemia. It should be emphasized that iron therapy must be restricted to patients with well-defined iron deficiency. Treatment with iron salts in other conditions may not alone be futile, but potentially harmful. It has become increasingly apparent that increased iron absorption characterizes a variety of hemolytic disorders and chronic refractory anemias. The quantity of iron present in the tissues in many cases of exogenous hemochromatosis occurring in these conditions exceeds that which can be accounted for by transfusion. Thus, in a patient with fatal Cooley's anemia, with severe hemochromatosis, who during childhood had received prolonged iron medication, 27 grams of iron were found in the liver, as compared with 6 grams introduced by transfusion.

For megaloblastic anemia of infancy a response is attained with folic acid or its biologically active form—citrovorum factor (folinic acid) or by liver extract, although it is recognized that ascorbic acid and vitamin B_{12} play a part in its causation and occasionally in its cure. May and his associates[13] from clinical evidence and the development of megaloblastosis in monkeys, have shown that the disease in infancy results from a primary folic acid deficiency which is intensified by a lack of ascorbic acid. A recommended schedule of treatment in this disease includes the daily administration of 15 mg. or more of folic acid by mouth together with ascorbic acid in a dosage of 200 mg.[14] It has been suggested that the addition of crude liver extract in a dosage of 10 to 15 units, given by injection once daily for a week, reinforces the action of folic acid.

It will be observed that the anemias for which transfusions are indicated consist of two groups: Those in which this measure constitutes a temporary expedient until spontaneous recovery sets in; and those in which, in the absence of specific therapy, the need for restoration of optimal blood levels is continuous and urgent. As for splenectomy, its value in the relief of congenital spherocytic anemia has been unequivocally established whereas in the remainder of the group (Table V) this procedure may lessen the anemia or reduce the hemolytic component when the factor of hypersplenism appears to be involved. Increases in hemoglobin, red blood cells and a rise in reticulocytes have been reported

with the use of ACTH and cortisone[15] and have, therefore, been employed where these objectives were desired. Except as they affect the underlying disorder, however, they are of questionable value. The decrease in blood destruction observed in hemolytic processes by altering immune reactions with inhibition of abnormal antibody has led to the successful employment of the steroids in the management of acquired hemolytic anemia. Their usefulness in controlling the severe joint and abdominal pain during the crisis of sickle cell anemia as indicated in recent reports[16] awaits more extended trial. The bone marrow and peripheral blood response attained with these hormones in rare instances of pure red-cell anemia may categorize cases that are marked for eventual spontaneous recovery with or without splenectomy.

The subject of iron-deficiency anemia, the anemia of prematurity and the treatment of chronic anemias with transfusions and splenectomy play roles of increasing importance in infancy and childhood and deserve more extensive discussion.

Anemia of the Premature Infant

Iron-deficiency anemia occurs more commonly during infancy and early childhood than at any other age period. The factors involved in its genesis and their relationship to the size and lability of iron depots are significantly revealed in the development of the anemia of prematurity and of the hypochromic anemia occurring in the iron deficient infant.

The proneness of the premature infant to develop subnormal hemoglobin levels as compared with the full-term infant has led to many hypotheses concerning its pathogenesis. While no intrinsic defects in the iron metabolism of the premature infant are known, the anemia has been ascribed to a variety of causes such as smaller iron stores because of a curtailed fetal period of acquiring iron, an exaggeration of the same hematologic processes leading to anemia which operate in the infant born at term and to more rapid body growth with coincidental expansion of the blood volume and dilution of circulating hemoglobin.

To prevent these lowered blood levels iron salts alone or in conjunction with other hematinics have been given soon after birth. Despite the application of these measures in many groups of infants, there has been no unanimity of opinion as to their value. The problem of therapy hinges on an understanding of the many interrelated mechanisms that

play a role in the pathogenesis of this anemia. The assumption that the premature infant is deprived of iron for storage in the critical third trimester of pregnancy has been challenged by Widdowson and Spray.[17] They investigated the iron content of human fetuses and of full-term infants and found that no large stores of iron were accumulated before birth. Only a small percentage of total iron is stored in the liver and spleen, the major portion being located in the circulating hemoglobin. The contribution of these tissue stores containing readily available iron to hemoglobin synthesis cannot, however, be underestimated.

An important factor in the interpretation of blood levels in the premature and full-term infant stems from increasing evidence that erythropoietic activity of the bone marrow is normally suppressed in early infancy. Physiologic anemia of the newborn, of which anemia in the premature is an advanced form, may more properly be attributed to a depression of erythropoiesis and of hemoglobin synthesis during the first two or three months than to hyperhemolysis. From blood volume data and estimates of total circulating hemoglobin in full-term infants, Gairdner, Marks and Roscoe[18] concluded that the blood levels during the neonatal period resulted from a gradual fall in hemoglobin concentration accompanied by decreased erythropoiesis. Presumably the return of the total hemoglobin mass to amounts equal to normal at the age of two to three months resulted from the reutilization of iron released from the destroyed red cells. Similar observations were made in our laboratory in premature infants[19] by serial examination of the fetal and adult types of hemoglobin. Blood volume and hemoglobin determinations permitted the calculation of total circulating hemoglobin without the need for considering the factors of growth and hemodilution. It will be observed in Figure 1 which illustrates the typical pattern in the premature infant that for the first four to five weeks fetal and adult hemoglobin declined simultaneously coincidental with a drop in total circulating hemoglobin. At the end of this decline adult hemoglobin is again synthesized and this rise is accompanied by a transient elevation in fetal hemoglobin. As the normal or adult hemoglobin fraction rises a gain in total body hemoglobin is observed with the peripheral hemoglobin eventually reaching a plateau. At sixteen weeks the total amount of circulating hemoglobin is restored to initial birth values. It was noteworthy that during this cycle the survival of the red cells is reduced to approximately seventy-five to ninety days indicating moderately increased destruction,

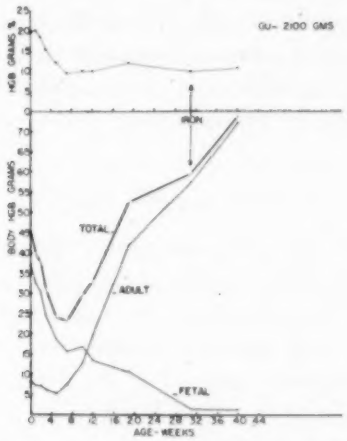

Fig. 1—*Note:* Upper graph indicates hemoglobin concentration in the peripheral blood in early infancy. Lower graph represents the changes in total circulating hemoglobin and its fetal and adult hemoglobin components. Note the initial drop in both types of hemoglobin and the resumption of adult hemoglobin formation at the end of this period. It is evident that there is abundant iron for hemoglobin synthesis for 16 weeks without the need of exogenous supplements.

a feature which may possibly differentiate the premature from the full-term infant.

Since storage iron appears to be adequate during this entire period with further increments supplied by whatever dietary iron is absorbed, it is questionable whether it is necessary to administer iron prophylactically to premature infants especially during a period when the bone marrow is non-reactive and when iron from degraded hemoglobin is being conserved. Published reports indicate that iron administered soon after birth fails to retard the postnatal drop in hemoglobin but reveals its effectiveness in higher values at about two or three months. There is need, however, for continued study to determine the merits of prophylaxis in the premature infant of low birth weight. In instances in which the hemoglobin drops to 7 grams or less between three to six weeks of age, transfusions are required, especially when the infant is listless, eats poorly and is not gaining. It should be mentioned, however, that besides the known complications of transfusions there is the possibility that the repeated administration of blood may suppress inherent

hematopoiesis at a time when the bone marrow has become responsive. For the present it seems preferable to prescribe iron only for those premature infants who show subnormal blood levels between two and four months of age when the adult type of hemoglobin is once more regenerated and to provide for the expanding hemoglobin mass incident to rapid growth.

Iron-Deficiency Anemia

Etiology: While iron unlike other food substances is not destroyed but constantly reutilized, the supply of this mineral becomes strained in age periods attended by unusual growth of blood volume such as occurs in infancy. As has been indicated in connection with the premature infant, the young organism exposed to the demands of rapid growth is particularly exposed to an anemia based on the exhaustion of storage iron for cellular and hemoglobin metabolism. Iron-deficiency anemia has a peak incidence between six months and two and one-half years when a number of circumstances combine to deplete available stores. These include inadequate antenatal storage from anemia in the mother, a diminished intake of dietary iron, infection and less commonly, blood loss. Infection which plays a dominant role as an etiologic factor in anemia in infancy and childhood frequently highlights an underlying state of iron deficiency. However, pallor, irritability, anorexia and gastrointestinal disturbances usually direct attention to severe grades of this disorder without complicating infection, although a history of repeated upper respiratory difficulties is not uncommon. Iron-deficiency anemia is observed in clinical practice in infants who are growing rapidly and who are fed on diets almost exclusively of milk and cereals with low iron content and who present feeding difficulties.

Treatment: That treatment with simple iron salts corrects the deficiency more promptly than the ingestion of foods rich in iron has been shown clinically and in the laboratory, and is related to the greater ease of absorption in the former.[20] Milk has usually been regarded at least theoretically as being an unfavorable vehicle for iron either through its combination with phosphates to form insoluble salts or because it shares with other foods of increased phosphorus content a basic difficulty in absorbing iron.[21] In Table VI are enumerated the iron content and dosage of common preparations employed in the treatment of iron-deficiency anemia in infancy and childhood. Ideal treatment consists of

TABLE VI—IRON THERAPY

Metallic Iron Content

Ferrous Sulfate—U.S.P. (hydrous) 20%
Ferrous Sulfate—U.S.P. (exsiccated) 37%
Iron and Ammonium Citrate—U.S.P. 14.5%-16.5%
Ferrous Gluconate—N.F. 12%

Dosage

1. *Ferrous Sulfate*
   a) Feosol—each 3 grain tablet contains 63 mg. elemental iron
      Dose: 2-4 tablets daily
   b) Elixir ferrous sulfate 4 cc.=32 mg. Fe
      Dose: 12 cc.=96 mg. Fe
   c) Fer-in-sol—0.6 cc.=15 mg. Fe
      Dose: 1.2 cc. x 3 daily=90 mg. Fe
2. *Ferrous Gluconate*
   5 grain tablet contains 34 mg. Fe
   Dose: 3 tablets daily
3. *Iron and Ammonium Citrate*
   7½ grain capsule=75 mg. Fe
   Dose: 2 capsules daily

Minimal daily dosage elemental Fe 100—200 mg.

the administration of a soluble ferrous salt, given in divided dosage preferably between meals.

Since a low hemoglobin constitutes the outstanding feature of anemias in early life, the observed response to a therapeutic trial of iron serves to eliminate those disorders which simulate nutritional iron-deficiency anemia. Many diagnostic features delineate the hematologic picture of an anemia due to a primary deficiency of iron, the simplest is the presence of microcytic hypochromic red cells which dominate the stained blood smear. Contributory evidence of diminished iron stores may be directly determined by bone marrow examination which reveals a decrease of non-hematin iron staining inclusions in normoblasts (sideroblasts)[22] and an almost complete absence of stainable iron or hemosiderin in marrow aspirates in contrast with increased quantities noted in infection and in the hemolytic anemias.[23, 24]

Iron Transport: Serum Iron and Iron-Binding Capacity: Recent studies dealing with the metabolism of iron with respect to the phases of absorption, transport and storage have provided another diagnostic tool in differentiating an anemia based on iron deficiency. Absorbed iron is transported in the plasma in combination with a specific protein, a beta$_1$ globulin variously designated as metal-combining globulin, siderophilin or transferrin whose movement is responsible for the redistribution of iron in the body. In the process of iron turnover this globulin delivers the metal to tissues either for storage or for hemoglobin synthesis and erythropoiesis. Normally transferrin is about one-third saturated, the bound fraction representing the segment linked to iron as serum iron. The unsaturated or latent capacity of this protein to combine with additional iron is subject to measurement. Serum iron is defined as the acid-soluble iron in the serum, the latent iron-binding capacity as that amount of additional iron capable of being bound by the unsaturated protein in serum and the total iron-binding capacity as the sum of these two components. The percentage saturation represents the percentage of iron-binding protein which is saturated with iron and is calculated by dividing the serum iron by the total iron-binding capacity. The total iron-binding capacity constitutes in effect an indirect estimate of the circulating iron-binding protein.

The level of serum iron reflects the balance between the iron absorbed, the iron utilized for hemoglobin synthesis, the iron released by red cell destruction and the size of the storage depots. More simply stated, at any particular time, the serum iron concentration represents a precise equilibrium between the iron entering and leaving the circulation. In iron-deficiency anemia, the depleted stores are represented by a greatly reduced serum iron, a markedly expanded iron-binding capacity and a very low percentage saturation. An increase in the total iron-binding capacity may be interpreted as an added facility for transporting this metal and is, therefore, an indication for iron therapy to replenish stores. In acute and chronic infection the impairment of hemoglobin synthesis is accompanied by a disturbance in erythropoiesis and a diversion of iron to tissue stores.[25, 26] Both the serum iron and the latent iron-binding capacity are significantly reduced but the percentage saturation is not decreased to the extent noted in iron-deficiency anemia. In disorders in which hemoglobin synthesis and marrow function are depressed as in untreated pernicious anemia, hypoplastic and aplastic

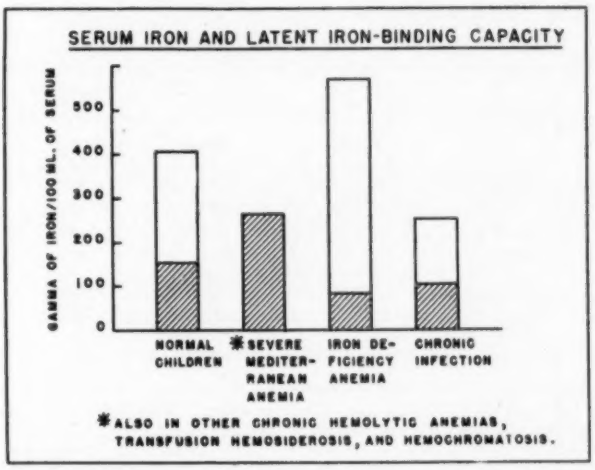

Fig. 2—Shaded areas represent serum iron, clear areas latent iron-binding capacity. The total iron-binding capacity is the sum of these two fractions. The high serum iron and absent latent iron-binding capacity in the hemolytic anemias are contrasted with the low serum iron and greatly expanded latent iron-binding capacity in iron deficiency anemia.

anemia, the serum iron is greatly elevated and the latent iron-binding capacity is reduced and often absent when multiple transfusions have been given. In conditions of iron excess such as the hemolytic anemias, transfusion hemosiderosis and hemochromatosis, the body iron is markedly increased as a result of the preponderance of red cell destruction over formation and in part from increased iron absorption. Here the serum iron is markedly elevated, the latent iron-binding capacity is absent so that the saturation is 100 per cent. As shown in Figure 2, the examination of the individual patterns materially advances the differentiation of the various anemias and provides an insight into the separate phases of iron metabolism.

Table VII lists the values for serum iron and iron-binding capacity in normal infants and children at various ages.[27] The iron values noted in the period from five to eight days represent a persistence of the findings in cord blood, namely, a higher serum iron and lower latent and total iron-binding capacities as compared to the normal serum iron and higher latent and total iron-binding capacities in the mother. These

TABLE VII—SERUM IRON AND IRON-BINDING CAPACITY—NORMAL VALUES

		S.I.	*L.I.B.C.*	*T.I.B.C.*	*% Sat.*
Adults		100	200	300	34
Infants	5-8 Days	148	114	262	65
	1-6 Mos.	132	279	412	32
	6-12 Mos.	106	323	429	25
	1-2 Years	95	319	414	22
Children	2-6 Years	116	279	395	28
	6-12 Years	127	213	340	38

All values in terms of micrograms/ 100 cc. serum

S.I. = Serum iron L.I.B.C. = Latent iron-binding capacity T.I.B.C. = Total iron-binding capacity
% Sat. = Percentage saturation

findings represent the combined effects of transplacental iron transfer to build up fetal stores as well as of the retardation of hemoglobin production occurring in the neonatal period. At about the end of the first month, erythropoietic function returns and the movement of stored iron in the direction of the bone marrow results in a low serum iron and high latent and total iron-binding capacities most marked at two years of age. This pattern, consistent with an iron-deficiency state despite the absence of anemia, indicates a continuous drain on storage depots. As already indicated, overt anemia occurs with rapid growth, dietary deficiency and other causative factors in which case the serum iron shrinks further and the latent iron-binding capacity expands.

Serum iron and iron-binding determinations may be employed as useful guides in gauging the adequacy and completeness of therapy in iron-deficiency states. Iron administered orally or parenterally in iron-deficiency anemia is utilized quantitatively for hemoglobin synthesis. If iron is administered parenterally only in amounts calculated to restore blood values to normal, or if oral therapy is terminated as soon as normal levels are reached, the iron stores remain unreplenished. The coexistence of normal hemoglobin values with incompletely filled depots is illustrated in Figure 3, in an infant who was treated with iron by mouth. There was an initial moderate drop in the latent and total iron-binding capacities with a minimal change in the serum iron. After a lapse of nine

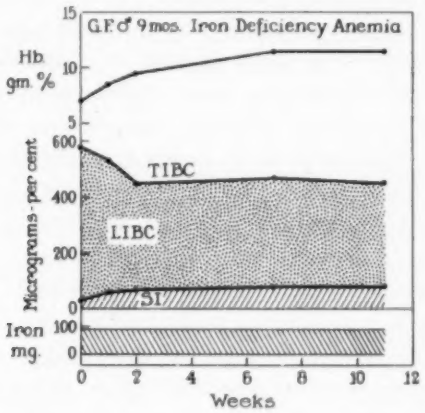

Fig. 3—Note that while iron by mouth results in a rise of the hemoglobin to normal levels the low serum iron and high latent iron-binding capacity reflect depleted tissue stores.[37] Reprinted by permission of The Year Book Publishers, Inc.

weeks, despite a rise in hemoglobin, the values for serum iron and iron-binding capacity remained fairly constant indicating the persistence of iron deficiency. In general, with adequate therapy the latent iron-binding capacity gradually falls and the serum iron gradually rises, not reaching normal values until both hemoglobin and tissue stores have been restored to optimal levels. To accomplish these objectives when measurements of serum iron and iron-binding protein are not available, the most practical procedure is to repeat hemoglobin determinations periodically even after normal values have been achieved with iron and to repeat this therapy when hemoglobin levels tend to drop.

Transfusions in Chronic Anemias: Depression of Erythropoiesis

So widespread is the use of transfusions for all classes of anemia, and so gratifying are the results in expeditiously restoring blood levels, that its limitations and hazards are frequently minimized and overlooked. Experience for the past ten years with a group of chronically anemic children in the Out-Patient Transfusion Clinic at The New York Hospital has provided an opportunity to test the effectiveness of periodic transfusions in maintaining optimal blood levels. The patients in this

group include chiefly those with severe Mediterranean anemia and in smaller numbers, cases of sickle cell anemia and pure red-cell or chronic aregenerative anemia. The many advantages of transfusing at regular intervals on an ambulatory basis rather than with repeated hospitalizations have been abundantly affirmed. One of the major difficulties, however, in the conduct of these clinics is to determine the level of hemoglobin at which blood is to be given, especially with the knowledge that in the chronic anemias normal levels achieved by transfusion are short-lived.

The failure to obtain sustained elevation of blood levels in chronic hemolytic and refractory anemias, stems basically from intrinsic defects in red cell formation, to some degree from hemolysis and lastly to the possibility that multiple tranfusions may depress endogenous blood production. The retarding effect upon erythropoiesis and hemoglobin synthesis can be readily discerned in patients with severe Mediterranean anemia who receive transfusions at two to three week intervals over a period of years. In these cases the diminished number of red cells characteristic of this disorder are to be found in the blood smear, the reduced concentration of fetal hemoglobin and a shift towards normal red cell resistance in fragility tests can be explained both by dilution with donor cells and by a specific depression of erythropoiesis. That transfusions tend to suppress bone marrow activity was known in the era before specific therapy was introduced in pernicious anemia. Robertson[28] noted in 1917, for instance, that a feebly reacting marrow could be markedly depressed by the sudden introduction of a large volume of blood into the circulation, and therefore, suggested the advisability of small transfusions. The suppressive effects on bone marrow induced by multiple transfusions have been documented by a growing body of evidence from experimental and clinical sources.[29, 30] We have two sets of observations from our laboratory which provide evidence that transfusions administered at frequent intervals tend to depress blood formation. These data were obtained in a small group of children with severe Cooley's anemia, in whom transfusions could be interrupted following splenectomy. We found that the production of fetal hemoglobin in excessive amounts, which characterizes the severe form of this disease, was greatly depressed during the period of active transfusion therapy, and that this was resumed at its termination. In two patients, the percentage of fetal hemoglobin, while receiving blood at two-week intervals, ranged from

16 to 21 per cent in one, and 18 to 23 per cent in the other. Following withdrawal of transfusions in the post-splenectomy period, these values rose to 62 per cent and 74 per cent respectively. In another group of experiments, we followed the survival of transfused erythrocytes in connection with blood volume determinations in three of these patients, so that the total red cell mass and circulating hemoglobin of the recipient could be measured. Analysis of the data revealed that following a transfusion, depression of erythropoiesis and hemoglobin synthesis occurred, which extended from the first to the seventh week with the sharpest decline at four weeks. Such observations do not detract from the necessity of transfusing patients with chronic anemia, but emphasize the advisability of occasionally withholding treatment even at sub-optimal levels. The hemoglobin value at which a transfusion is indicated in chronic anemias, cannot be arbitrarily fixed but varies with the associated signs and symptoms manifested by the individual patient. As a guide to management, we have found that with few exceptions, patients with a severe Mediterranean anemia do not require transfusions until hemoglobin levels drop to 7 to 7.5 grams or below, at which point clinical symptoms usually appear. While blood levels in children with this disorder continue to decline progressively without treatment, the patient with sickle cell anemia must be viewed differently. In the latter the need for blood is much less urgent, since hemoglobin levels usually tend to stabilize in a range between 6 and 7 grams without distressing symptoms and regardless of treatment.

While these remarks have emphasized the benefits of curtailing transfusions in the chronic hemolytic anemias, there is the possibility that this policy is not without theoretic harm. It has been pointed out that in Cooley's anemia[31] excessive body iron accumulating from multiple transfusions does not lead to the pathologic changes indicative of hepatic cirrhosis and pancreatic hemochromatosis without the intervention of an accessory factor. It has been postulated that long continued tissue hypoxia in patients whose lives are prolonged by transfusion therapy may be ultimately responsible for this progression. From this standpoint, transfusions above sub-optimal levels may conceivably retard the development of visceral fibrosis by increasing oxygen tension, although contributing simultaneously to the iron overload. While the application of such a program may not be entirely practical, some modification is worthy of further investigation.

TABLE VIII—SPLENECTOMY IN CONGENITAL SPHEROCYTIC ANEMIA
(1950-1953)

		Pre-Splenectomy For 1 Year Prior to Operation			*Post-Splenectomy*		
Patient	*Age at Present*	*Age at Splenectomy*	*Hb Average (gm.)*	*Transfusions*	*Period of Follow Up*	*Present Hb (gm.)*	*Transfusions*
1. NN	8 yrs 8 mos	5 yrs 8 mos	8.3	12	3 yrs	13.0	0
2. BD	15 yrs 5 mos	12 yrs 10 mos	10.9	0	2 yrs 7 mos	14.1	0
3. TD	12 yrs 9 mos	10 yrs 2 mos	10.3	0	2 yrs 7 mos	13.6	0
4. LA	11 yrs 3 mos	9 yrs 2 mos	9.7	0	2 yrs 1 mo	14.5	0
5. PL	5 yrs 8 mos	4 yrs 1 mo	7.4	1	1 yr 7 mos	15.1	0
6. RL	8 yrs 4 mos	7 yrs 2 mos	9.2	4	1 yr 2 mos	14.8	0
7. AS	14 yrs 1 mo	13 yrs	8.0	0	1 yr 1 mo	15.3	0
8. TC	4 yrs 10 mos	3 yrs 9 mos	6.9	0	1 yr 1 mo	13.3	0
9. RD	5 yrs 9 mos	5 yrs 2 mos	9.3	3	7 mos	12.0	0

SPLENECTOMY

Hypersplenism: The mechanisms implied in the concept of hypersplenism provide a plausible explanation for the pathogenesis of a group of hematologic syndromes which are characterized by a reduction of one or more cellular elements in the peripheral blood with compensatory hyperplasia in the bone marrow of the corresponding cells, and the expectation that the disorder will be corrected by splenectomy. These dyscrasias have been attributed to either an overactive and unusually enlarging spleen, in which either selective storage and increased destruction of blood cells occurs, or in which the organ exerts an inhibitory influence upon a normal or hyperactive bone marrow. In either case removal of a presumably abnormally functioning spleen has been shown to restore normal blood levels with varying degrees of success. The graded responses can be exemplified by the results attained in congenital spherocytic anemia and in severe Mediterranean anemia in both of which we have recently had a concentrated experience on the Pediatric Service of The New York Hospital.

Congenital Spherocytic Anemia: In Table VIII are recorded nine cases of congenital spherocytic anemia in children ranging in age from

four to thirteen years in whom splenectomy led to a complete clinical and hematologic recovery. The fact that the principal hemolytic focus resides in the spleen is corroborated by the absence of anemia following its removal although spherocytes persist in the peripheral blood. The exact manner in which these remedial changes are brought about is not entirely understood. There is strong evidence[32] that these erythrocytes, because of their globular shape are trapped in splenic pulp where they undergo lysis and that prolongation of this process results in enlargement and overactivity of the spleen. So beneficial is splenectomy in this disorder that this procedure is strongly recommended in all patients regardless of age, just as soon as diagnosis is firmly established.

Mediterranean Anemia (Cooley's Anemia, Thalassemia): In other blood disorders splenectomy is undertaken for the relief of urgent symptoms traced to a pathologically overactive organ in which no other remedial therapy is available. Severe Mediterranean or Cooley's anemia falls into this category in the stage when an enlarged and burdensome spleen and the excessive transfusion requirements coexist. While the fundamental defect in this disease is intracorpuscular and related to an inherited abnormality in hemoglobin synthesis a hemolytic component eventually supervenes which aggravates the anemia. The hyperactivity of the spleen which contributes to the severe anemia is probably based on anatomical derangements resulting from the impact of continuous exogenous and endogenous blood destruction on inadequately oxygenated tissue. This extracorpuscular defect was recently demonstrated by Lichtman and his co-workers[33] who noted a shortened survival of transfused blood in patients with splenomegaly and a reduction of transfusion requirements in most instances following splenectomy.

In Table IX are summarized the results of splenectomy carried out since 1949 in ten cases of severe Mediterranean anemia. While these patients have not been followed for sufficient time to permit final evaluation of the results, it is apparent that transfusion needs were strikingly reduced especially in the older child and this was usually accompanied by amelioration of clinical symptoms. In some of the younger patients the liver increased in size and bone pain recurred subsequent to operation, but here too the demand for transfusions was noticeably lessened. Possibly the favorable results with splenectomy can be ascribed in part to the more comprehensive treatment of the disease in recent years, especially in relation to infection and cardiac dysfunction to which these

TABLE IX—SPLENECTOMY IN COOLEY'S ANEMIA (1949-1953)

		Pre-Splenectomy For 1 Year Prior to Operation				*Post-Splenectomy Entire Post-Operative Period*	
Patient	*Age at Present*	*Age at Splenectomy*	*Hb Average (gm.)*	*Transfusions*	*Period of Follow Up*	*Average Hb (gm.)*	*Transfusions*
1. DB*		5 yrs 10 mos	7.5	39	1 yr 3 mos	8.4	24
2. SS	15 yrs 6 mos	11 yrs 8 mos	8.0	30	3 yrs 10 mos	8.1	26
3. AV**	15 yrs 11 mos	13 yrs 5 mos	6.8	30	2 yrs 6 mos	8.5	12
4. DE	9 yrs 3 mos	7 yrs 9 mos	5.7	35	1 yr 6 mos	7.9	15
5. JP	15 yrs 2 mos	13 yrs 8 mos	6.7	33	1 yr 6 mos	9.9	4
6. JN	9 yrs 6 mos	8 yrs 4 mos	6.1	29	1 yr 2 mos	8.7	18§
7. RP	16 yrs 10 mos	15 yrs 8 mos	6.9	29	1 yr 2 mos	8.8	1§
8. MG	3 yrs 10 mos	3 yrs 3 mos	6.6	28	7 mos	8.0	2
9. FG	8 yrs 4 mos	7 yrs 10 mos	6.4	27	6 mos	8.2	3
10. AD	17 yrs 9 mos	17 yrs 6 mos	7.6	21	3 mos	8.9	0

* Patient died of encephalitis (?) in Aug. '50 in another hospital.
** Sickle cell-Mediterranean anemia disease.
§ Includes transfusions for study—i.e., red cell survival, blood volume, etc.

patients are susceptible. In evaluating results it must also be borne in mind that each case of Mediterranean anemia must be judged individually because of the wide range of severity of this disorder.

The indications for operation consist of massive enlargement of the spleen to a degree where discomfort arises from its mechanical presence, when the functioning of adjacent organs is impaired and when there is a need for transfusions at increasingly frequent intervals to maintain suboptimal hemoglobin levels. The increase of nucleated red cells in the peripheral blood following splenectomy is most marked in this disease and may reflect the removal of an inhibitory influence from the bone marrow where these cells predominate. As corroborative evidence for this relationship was the finding in three instances, in which this examination was carried out, of a sharp drop in the percentage of these cells in the bone marrow for varying periods following the operation. In these patients, the values for nucleated red cells, ranging from 60 to 83 per cent preoperatively, were reduced to 12 to 28 per cent for several weeks postoperatively. This decrease, however, was not maintained for any

appreciable period. In the determination of maintenance requirements (a level of 7 grams of hemoglobin) and to assess the suppressive effects of repeated transfusions, it is important to test the patient's inherent capacity for hemoglobin synthesis by occasionally withholding treatment in the absence of distressing symptoms. Removal of a hemolytic organ is a major consideration in the older adolescent approaching adult life where it is hoped that hemoglobin synthesis would subsequently be stabilized at levels compatible with basic metabolic needs without resort to transfusions. While striking improvement often follows splenectomy for varying periods in younger children when the indications are fully met, it is our impression that more lasting benefits are obtained in patients from the age of puberty. Definite criteria for splenectomy, however, await extended experience particularly with the employment of more refined techniques such as preoperative red cell survival studies and of long term study of the individual patient.

It is noteworthy that the objective of maintaining suboptimal hemoglobin levels with limited transfusions following splenectomy is not without its shortcomings. For example, the occurrence of severe skeletal pain, especially in the lower extremities encountered in certain patients (J.P. and A.D., Table IX) postoperatively may be attributed to the need for maximal erythropoiesis within the bone marrow when transfusions are no longer administered. It should be stressed also that success from this operation cannot be measured entirely in terms of reducing the number of transfusions, since discomfort and pain may be frequently alleviated by administering blood when anemia is only of moderate degree. In the last analysis the optimism generated by this and contemporary reports must be tempered by the knowledge that in Mediterranean anemia, splenectomy represents a palliative measure and that the ultimate cure depends on the discovery of the exact nature of the intracorpuscular defect and its specific correction.

Summary

The shifting background of blood levels inherent in the growth of infants and children requires that abnormal values be interpreted in terms of the normal range for the corresponding age period. The appraisal of a specific blood response is also enhanced by an inquiry into fetal conditioning factors as well as hematopoietic influences which operate in the postnatal period, and in the remainder of infancy and childhood.

Many of the complexities relative to diagnosis may be resolved by coordinating the information derived from a variety of interrelated sources. While technical advances have been numerous in recent years, the detection of the common anemias lies within the province of every medical practitioner by careful history and physical examination, and with the use of simple instruments and procedures.

The utilization of the more elaborate techniques permits a broader visualization of physiologic forces controlling blood formation and their aberrations. Certain data acquired with these added facilities have been reviewed from the standpoint of their therapeutic implications. These included the dynamic aspects of iron metabolism in the premature, the correlation of hemoglobin levels with the state of iron stores in iron-deficiency anemia, the characteristic patterns of serum iron and iron-binding capacity in this and other anemias, the suppressive effects of multiple transfusions in chronic anemias, and the indications for removal of the spleen in two diverse hemolytic disorders: congenital spherocytic anemia and severe Mediterranean or Cooley's anemia.

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THE THROMBOCYTOPENIC PURPURAS*

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THROMBOCYTOPENIC purpura may occur in all grades of severity. At one extreme, it may be merely a slight exacerbation of the easy bruising tendency of some individuals whom we consider normal. At the other, it may be fulminating in its onset and devastating in its consequences. The former is usually of minor clinical significance, the latter represents a medical emergency. The symptoms and signs of this disorder are given in the first table (Table I). Certain comments may be made. First of all, the tendency is for the lesions to occur in the more dependent areas probably as the result of increased intravascular pressure in these areas. Secondly, there is a notable difference from hemophilia in the matter of hemarthroses. These are uncommon in thrombocytopenia. In the case of intracranial bleeding, this occurs more frequently in this hemorrhagic disorder than perhaps in any other one.

Because splenectomy may be extremely beneficial in some of these patients and extremely harmful in others, the differential diagnosis becomes particularly important. I have attempted to classify these diseases in three ways. First of all, there is an etiological classification (Table II) which will be dependent upon a careful history and physical examination and a complete hematological work-up. By the term infectious purpura is meant the thrombocytopenia associated with certain infectious diseases. Not only are the overwhelming bacterial infections so complicated but more recently thrombocytopenia has been noted to be a complication of milder diseases such as rubella and infectious mononucleosis. It will be noted that the commonly employed classification of thrombocytopenic purpuras into "primary" and "secondary" types has been discarded for much the same reason that "primary" and "secondary" anemias are no longer used. For thrombocytopenia due to intrinsic disease of the marrow or spleen the terms "myelopathic" and "splenopathic" have been employed.

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TABLE I—SYMPTOMS AND SIGNS OF THROMBOCYTOPENIC PURPURA

1. Ecchymoses, purpura and petechiae in skin and mucous membranes. Particularly dependent areas.
2. Intractable bleeding from small wounds.
3. Intractable bleeding from mucous membranes—epistaxis, menorrhagia, hematuria, hematemesis, melena, bleeding gums.
4. Hemarthroses uncommon.
5. Intracranial bleeding not uncommon.

TABLE II—ETIOLOGICAL CLASSIFICATION OF THROMBOCYTOPENIC PURPURA

1. Idiopathic (Werlhof's Disease).
2. Infectious.
3. Toxic.
4. Allergic.
5. Myelopathic.
6. Splenopathic.

A second classification may be attempted on the basis of the morphological examination of the bone marrow aspirate (Table III). Such an examination is indispensable in the complete work-up of any patient with thrombocytopenia. Attention is called to the fact that a marrow which shows normal megakaryocytes may be grossly pathological in other regards. Still a third classification may be attempted on the basis of whether or not the spleen is significantly enlarged (Table IV). To all these forms of thrombocytopenic purpura must be added the rare disorder thrombotic thrombocytopenic purpura characterized by a fever and by a fulminating, almost invariably fatal course. This rare disease can only be diagnosed by demonstration of capillary thrombi in biopsied tissues ante-mortem and will not be discussed further in this paper.

The laboratory demonstration of thrombocytopenia is often not as easy as it sounds. Platelets have a propensity for agglutination and this may make certain areas of the blood smear relatively free of platelets or may diminish the accuracy of counting platelets in a hemocytometer. Then the recognition of platelets may be difficult since they are only a few micra in diameter and may be easily confused with other particulate

TABLE III—CLASSIFICATION OF THROMBOCYTOPENIC PURPURA ON BASIS OF MORPHOLOGICAL EXAMINATION OF BONE MARROW

1. Megakaryocytic (megakaryocytes normal or increased).
   a) Qualitative changes in megakaryocytes may be detected.
   b) The remainder of the marrow may be normal, may show eosinophilia, *or may be pathological.*
   c) When remainder of marrow is normal or eosinophilic, diagnosis is most likely idiopathic or allergic thrombocytopenia but may also be infectious or toxic.

2. Amegakaryocytic (megakaryocytes reduced to absent).

Leukemia	Tuberculosis
Pernicious anemia	Carcinomatosis
Aplastic anemia	Lymphomatosis
Chronic hypochromic anemia	Myelomatosis, etc.

TABLE IV—CLASSIFICATION OF THROMBOCYTOPENIC PURPURA ON BASIS OF SPLEEN SIZE

1. Splenomegalic

Leukemia	Tuberculosis
Congestive splenomegaly	Disseminated Lupus Erythematosus (L. E. cells in marrow)
Gaucher's Disease	Sarcoid
Felty's Syndrome	
Lymphomatosis	

2. Non-splenomegalic

Idiopathic	Toxic
Infectious (Sometimes slightly enlarged)	Allergic

material. The laboratory tests primarily relating to thrombocytopenia have been summarized (Table V). It is well known that many patients with thrombocytopenia show increased capillary fragility and a prolonged bleeding time (Table VI). We have preferred the tourniquet test and have standardized it at 100 mm. mercury for ten minutes.

Because time does not permit a complete discussion of the pathogenesis of the toxic, infectious, allergic, myelopathic and splenopathic thrombocytopenic purpuras, most of the remainder of this paper will be devoted to a discussion of idiopathic thrombocytopenic purpuras about which much has been learned in recent years. As may have already been deduced, the diagnosis of this disease is largely made by exclusion. To put it another way, if there is no recent history of infection or drug

TABLE V—LABORATORY TESTS FOR THROMBOCYTOPENIA

1. Direct counting in hemocytometer
   a) Rees and Ecker
   b) Pohle modification
   c) Brecher and Cronkite modification using phase microscopy
2. Indirect counting
   a) Dameshek method
   b) Ordinary blood smears
3. Clot retraction
   a) Aggeler semi-quantitative modification
   b) MacFarlane semi-quantitative modification
4. Prothrombin consumption (may be disturbed in other hemorrhagic diseases).

TABLE VI—LABORATORY FINDINGS ASSOCIATED WITH SEVERE THROMBOCYTOPENIA*

1. Increased capillary fragility
   (a) positive tourniquet test
   (b) positive suction test
2. Increased bleeding time

* The above may be abnormal in non-thrombocytopenic disorders.

ingestion, accidental, therapeutic or occupational exposure to metals aromatic chemicals, or irradiation, if there is no apparent relationship to an antigen, if the spleen is not enlarged, and if the bone marrow is relatively normal in appearance, the diagnosis of idiopathic thrombocytopenic purpura should be entertained. The age and sex distribution have been determined from 737 patients in the recent literature reported to have this disorder (Tables VII and VIII). It is apparent that children and adult females are most susceptible to this disorder.

The most recent studies in this disorder have implicated the existence of a humoral substance, probably an antibody, in the plasma. Such a humoral substance was suggested by Epstein and coworkers who observed seven pregnancies occurring in five mothers with thrombocytopenia. Six of the seven children had transient thrombocytopenia. This was the situation whether or not the mothers had been splenectomized prior to delivery.

TABLE VII—AGE AND SEX DISTRIBUTION OF IDIOPATHIC THROMBOCYTOPENIC PURPURA—737 PATIENTS

Age	*Sex* *F*	*M*	*Total*
0-15 years	188	147	335
16 years and older	317	85	402
Sex Ratio:	*F*	*M*	
0-15 years	1.3:	1	
16 years and older	3.7:	1	

TABLE VIII—AGE DISTRIBUTION OF IDIOPATHIC THROMBOCYTOPENIC PURPURA—737 PATIENTS

Patients	
0-15 years	45%
16 years and older	55%
Population	
0-15 years	24%
16 years and older	76%

TABLE IX—SPECULATIONS CONCERNING ROLE OF SPLEEN IN PATHOGENESIS OF IDIOPATHIC THROMBOCYTOPENIA

1. Site of formation of platelet agglutinins (in some patients agglutinins persist following splenectomy).
2. Removal of "sensitized or agglutinated" platelets.
3. Secretion of substance interfering with maturation of megakaryocytes and release of platelets.
4. Direct or indirect influence on capillary fragility.

A review of the literature concerning other pregnancies in thrombocytopenic women showed that whether or not the mother still possessed her spleen at the time of delivery, the large majority of infants had thrombocytopenia at birth. It was concluded that some humoral substance independent of the spleen was transferred across the placenta into the fetus producing thrombocytopenia. Recent studies have led to the

TABLE X—PRESENT DAY THERAPY OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

1. Conservative or expectant management.
2. Corticotropic or adrenocortical hormones.
3. Splenectomy.
4. Transfusions
   (a) Whole blood (to combat blood loss and shock).
   (b) Platelet-rich polycythemic blood.*
   (c) Platelet-rich plasma or platelet suspensions.*

*Requires siliconized apparatus.

hypothesis that this substance may well be a platelet agglutinin. Evans and his associates were probably the first to demonstrate a platelet agglutinating factor in the serum of some patients with thrombocytopenic purpura. Harrington and his coworkers observed at the same time that the transfusion of blood or plasma from most patients with thrombocytopenia into normal non-thrombocytopenic subjects transiently decreased the platelet counts of the recipients. Some of Harrington's patients retained the thrombocytopenic factor in their plasma after their spleens had been removed. Another approach to this study has been via studies on the survival of platelets transfused into patients with thrombocytopenia. Platelet survival time in the recipient may be either short or long. When it is short it is felt that the recipient's thrombocytopenia is due to an increased rate of destruction of platelets. When it is long, decreased production of platelets may be the mechanism involved in the pathogenesis of the recipient's thrombocytopenia. All recent studies of platelet transfusions have shown that the survival time of transfused platelets into either normal or thrombocytopenic recipients becomes progressively decreased with each successive transfusion. This seems to be due to the development of platelet agglutinins and is of considerable importance in that it may limit the therapeutic usefulness of platelet transfusions or platelet rich blood in thrombocytopenic patients.

As mentioned above, capillary fragility frequently accompanies thrombocytopenia. Several investigators called attention to the fact that splenectomy and perhaps also other operations, may improve capillary

TABLE XI—SUMMARY OF VASCULAR AND PLATELET RESPONSE TO PREOPERATIVE ACTH AND TO SPLENECTOMY IN 7 PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

	Response to pre-op. ACTH		*Response to Splenectomy*	
	Vascular	*Platelets*	*Vascular*	*Platelets*
Patient 1	Complete	None	Complete	Complete
Patient 2	Complete	Partial	Relapse	Relapse
Patient 3	Complete	Complete	Complete	Complete
Patient 4	Complete	None	Relapse	Relapse
Patient 5	Complete	None	Complete	Complete
Patient 6	Complete	Partial	Complete	Complete
Patient 7	Complete	Complete	Partial	Partial

fragility either before platelets are increased in number or without any change in the number of platelets. Before the widespread usage of adrenal steroids, Robson in Scotland theorized that improvement in capillary fragility might be a nonspecific effect of operative interference. Robson in Scotland and Faloon and coworkers in this country then showed that the administration of cortisone or corticotropin regularly improved capillary fragility in thrombocytopenia regardless of etiology but only irregularly increased platelet counts and then several days after improvement in capillary fragility.

The present day speculations on the role of the spleen in the pathogenesis of idiopathic thrombocytopenic purpura have been summarized (Table IX).

Again, with regard to treatment little will be said in the matters of toxic, allergic or infectious purpura. Elimination of the offending drug or allergen and specific treatment, if available, for the underlying infection will usually result in a remission of the purpura. In general, if the marrow is of the amegakaryocytic variety, the primary condition responsible for this should be treated by any available means. To reiterate, if there is splenomegaly, the likelihood of the patient having idiopathic thrombocytopenia is minimal. However, in this situation when megakaryocytes are present in the marrow and the thrombocytopenia appears to threaten the life of the patient, splenectomy may be considered and may have transient beneficial effects. However, in many such situations,

TABLE—XII—RESULTS OF SPLENECTOMY FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA

(All ages, both sexes, acute and chronic, all severities)
(From Harrington, Robson, Rosenthal, Hirsch, Elliott, Wintrobe, J. Watson and Lozner)

Total	*Complete Remission*	*Incomplete Remission*	*Complete Failure*
303 (100%)	184 (61%)	52 (17%)	67 (22%)

TABLE XIII—MORTALITY (EARLY AND LATE) FOLLOWING SPLENECTOMY FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA

Total	*Deaths*
238 (100%)	26 (11%)

the underlying disease will be leukemia or lymphoma and the transient benefit to be achieved must be weighed against the operative risk and the underlying generalized malignant nature of the disease.

The present day therapy of idiopathic thrombocytopenic purpura is given (Table X). The patient's age represents an important factor in deciding upon treatment. The majority of children show a tendency to spontaneous remission. The older the patient, the less is this tendency. It is, therefore, believed that splenectomy in childhood should be reserved for uncontrollable bleeding or for chronic or recurrent thrombocytopenia. It is reassuring that cerebral vascular accidents are far less common in children than in adults. Nevertheless, they do occur and some observers believe that, during the period of expectant management, activity should be severely restricted and steroid therapy employed. In adults, despite the greater menace of a cerebral vascular accident, it is our opinion that a trial of a few months of conservative management is desirable in most patients. During this interval, hormonal therapy is frequently employed and transfusions are given as indicated. Rather few complete and permanent remissions have been obtained with hormonal treatment. Most patients will have a complete remission of the increased capillary fragility. Perhaps only one-half of the patients will have a satisfactory remission of the thrombocytopenia. Following discon-

tinuance of the hormones, both the capillary fragility and the thrombocytopenia usually quickly return to their previously disturbed levels in the vast majority of patients. Thus, these hormones have their greatest usefulness as an aid to expectant management and in the control of fulminating hemorrhage, particularly menorrhagia. We recently have been employing these hormones in the preoperative preparation of patients for splenectomy. At first we had hoped that remission with the use of hormones might have a high correlation with remission following splenectomy. This hope has not been achieved (Table XI). Although all of seven patients treated with ACTH showed improvement in vascular fragility, in three of these this improvement did not persist following splenectomy. Two patients showed no improvement in thrombocytopenia with ACTH but complete remission in this aspect of their disorder followed splenectomy. We were also interested in two other aspects of the use of ACTH prior to splenectomy. The first of these related to the management before and during the surgical procedure and the reduction of mortality during this procedure. Our initial impressions on this aspect are highly satisfactory but as in most situations with regard to mortality large numbers of patients will have to be treated before any conclusions can be reached. Secondly, we were concerned with the influence of ACTH on postoperative wound healing. No interference in this process has thus far been noted.

The crucial decision in the treatment of patients with idiopathic thrombocytopenic purpura concerns whether and when to subject the patient to splenectomy. The literature is quite contradictory with regard to the prognostic significance of the bone marrow. Our own results have been somewhat depressing on this point. Although large numbers of megakaryocytes and eosinophilia seemed to make the prognosis better, we have obtained good results following splenectomy when this situation did not obtain and we have had poor results following splenectomy when it did obtain. Other investigators have had the same experience. The situation with regard to splenectomy would be a great deal simpler if the percentage of cures were higher. In some early series, a cure rate of 95-98 per cent had been reported. It is obvious from later studies that these series did not take into consideration long follow-ups. An attempt has been made to summarize some of the recently reported experience on splenectomy (Table XII). In all, 303 splenectomies with good follow-ups were reviewed. Some of these were splenectomized early with

the philosophy that this might prevent further difficulty. Some were splenectomized late when medical treatment had failed. A few emergency splenectomies for fulminating hemorrhage are included. Not all of the authors included mortality statistics. From those that did the following data were collected (Table XIII). The data on splenectomy are most difficult to analyze. Although it is far from the cure-all it was once heralded to be it nevertheless is probably the treatment of choice in adults after a few months of expectant management and in children after approximately a year. The significance of accessory spleens in patients who fail to improve or who relapse following splenectomy is controversial. In most such patients they cannot be found at postmortem. They may be searched for ante-mortem by injecting intravenously colloidal thorium. This procedure too remains to be evaluated.

In summary, the differential diagnosis, pathogenesis and treatment of the thrombocytopenic purpuras have been reviewed. Three classifications have been presented, an etiological one, one based on morphology of the marrow and one based on spleen size. The diagnosis of idiopathic thrombocytopenic purpura is made by exclusion. The treatment of this disorder at first should be expectant and may include steroid hormones. If a remission does not occur, splenectomy remains the treatment of choice, will result in a "cure" of some 60 per cent, will improve another 20 per cent, but will fail in approximately 20 per cent.

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RECENT STUDIES IN PRIMARY PULMONARY HYPERTENSION

INCLUDING PHARMACODYNAMIC OBSERVATIONS ON PULMONARY VASCULAR RESISTANCE*

DAVID T. DRESDALE, ROBERT J. MICHTOM and MARTIN SCHULTZ

PRIMARY pulmonary hypertension appears to be diagnosed more frequently. It is distinguished from secondary pulmonary hypertension by the absence of any intrinsic heart or lung disease and by the absence of mechanical blocks in the pulmonary vascular bed seeded from without, e.g., pulmonary emboli. Cardiac catheterization, of course, has given impetus to this by making possible the measurement of pulmonary vascular pressures as well as by ruling out certain congenital deformities. Wood,[1] in England, found six cases which he classified as idiopathic pulmonary hypertension during a study of 233 unselected cases of suspected congenital heart disease, 152 of which were catheterized. Chapman[2] in a similar study so diagnosed two of seventy-two patients who had right heart catheterizations. It seems that many people working in cardio-pulmonary laboratories have had the experience of studying some patients with pulmonary hypertension and failing to establish the etiology of the hypertension despite careful evaluation by recognized clinical and physiological methods. However, primary pulmonary hypertension should not be a "waste paper basket" category into which are tossed all the apparently unexplained diagnoses of pulmonary hypertension. The syndrome of primary pulmonary hypertension is fairly distinct. The diagnosis should be made not only by a process of elimination but by looking for and recognizing the definite clinical characteristics of this syndrome of which the patho-physiological processes can be evaluated in the cardio-pulmonary laboratory.

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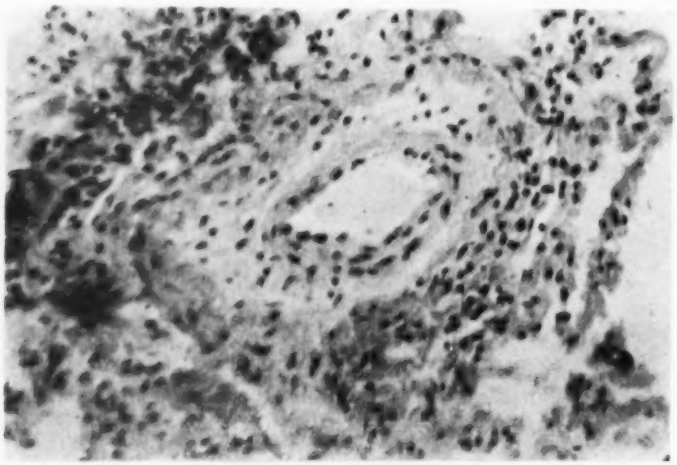

Fig.1—Marked intimal sclerosis of a small intrapulmonary artery is noted; X 500.
(See page 206 for permission to reproduce Figs. 1, 2, 4 and 5.)

Primary and secondary pulmonary hypertension are associated with right ventricular hypertrophy and also, in many instances, pulmonary vascular sclerosis. The etiology of pulmonary hypertension without any vascular changes as the cause of right ventricular hypertrophy had evoked much speculation prior to the cardiac catheterization era. De Navasquez and his associates[3] in 1940 preferred to designate their three autopsied cases with right ventricular hypertrophy and without abnormal pulmonary vascular changes as "idiopathic right ventricular hypertrophy" rather than introduce the concept of pulmonary hypertension. Soothill[4] in 1951 reported a case of primary pulmonary hypertension in a twenty-two year old male whose pulmonary artery pressure was 128/83 mm. Hg. At necropsy, the heart and lungs were sent to Dr. De Navasquez. The note that Dr. De Navasquez sent back describing the organs included the following statement: "The heart and lungs appeared to show the abnormalities usually associated with most cases of idiopathic right ventricular hypertrophy without any additional features."

All cases of primary pulmonary hypertension show marked right ventricular hypertrophy but the pulmonary vascular changes have not always been present. That pulmonary vascular changes may accompany

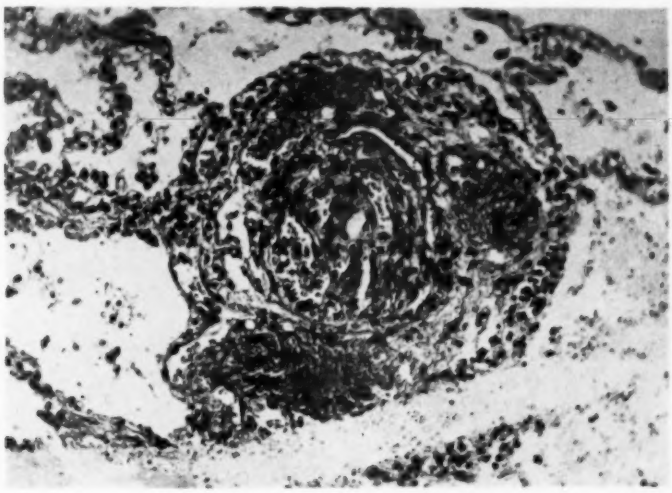

Fig. 2—A recanalized thrombus in a pulmonary vessel of microscopic size is seen; X 250.

prolonged pulmonary hypertension, not unlike the vascular changes seen in systemic hypertension, can be appreciated more readily by the following papers entitled: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle,[5] Primary Pulmonary Vascular Sclerosis,[6,7] Obliterative Pulmonary Arteriolosclerosis,[8] and so forth, which report autopsied cases that we feel fall into the category of primary pulmonary hypertension. The pulmonary vascular changes that occur are found proximal to the capillaries. When present, they have shown considerable variation in their nature, distribution, and severity. The predominant changes are atheromatous lesions of the stem and large elastic arteries, alone, or in conjunction with fibrous intimal thickening and narrowing (Fig. 1), or obliteration of the smaller arteries. Occasionally, medial hypertrophy has been described. Thrombotic lesions in various stages of organization have been seen in the precapillary and postcapillary vessels of microscopic sizes (Fig. 2).[9] When present, these lesions are seen much less frequently than the sclerotic changes. It is interesting that Rich[10] described similar thrombotic lesions in 90 per cent of the cases of tetralogy of Fallot that he studied. Lesions of a

similar nature have also been described in the pulmonary vessels of long-standing mitral stenosis with pulmonary hypertension.[11, 12] Dr. Rich felt that the lesions he described were due to the sluggish pulmonary blood flow and to the polycythemia. Decreased pulmonary blood flow is found in patients with pulmonary hypertension, either of the primary type,[4, 9] or secondary to mitral stenosis.[13-16] Thrombotic lesions, as mentioned before, coexist with extensive pulmonary vascular sclerosis. It is suggested, therefore, that these thrombotic lesions may be a result of the markedly narrowed vessels and the sluggish pulmonary blood flow.

Primary pulmonary hypertension is not limited to any age group, having been described in patients as young as twenty months[7] and found in the eighth decade.[8] The majority of cases, however, fall in the age group of twenty to forty years. There appears to be a slightly greater incidence in the female sex. That a familial tendency might exist is suggested by studies made possible through the courtesy of Dr. E. P. Maynard and Dr. W. Dressler on a mother, her sister, and her son. All had the criteria for the diagnosis of primary pulmonary hypertension. A brother of the mother is reported to have died of an undiagnosed heart disease at an early age. The mother died at the age of forty-three, the sister died at thirty-one, and the son died at twenty-one, all in severe right heart failure.

Congenital defects were ruled out in both the mother and son by right heart catheterization. Pulmonary function studies on the son were all within the normal range. His pulmonary artery pressure was 78/33 mm. Hg, his systemic pressure was 97/56 mm. Hg and his arterial oxygen saturation was 95 per cent. It was not possible to do pulmonary function studies on the mother. Her pulmonary artery pressure was 122/52 mm. Hg and at the same time her systemic pressure was 110/68 mm. Hg. Her blood oxygen saturation was 92 per cent at a time when she was deeply sedated. The sister's diagnosis was based solely on the clinical findings, as well as electrocardiographic and x-ray studies. Electrocardiographic changes in this syndrome are those consistent with right ventricular hypertrophy.

Primary pulmonary hypertension runs a malignant course characterized by right heart failure, not infrequently terminating in sudden death. The salient clinical features in order of their frequency are listed. 1) Exertional dyspnea and weakness, probably related to the decreasing cardiac output, are the most prominent symptoms and are present in all

the patients. 2) Exertional substernal and left chest pain, resembling angina, is present in approximately 25 per cent of the patients. This symptom has also been described by Viar and his associates[17] as occurring in some patients with secondary pulmonary hypertension. They felt that the most likely cause for the pain was the distention of the pulmonary artery. We had proposed in a former communication[9] on this subject that it might be due to a combination of severe right heart failure resulting secondarily in diminished left heart output and decreased coronary blood flow. The decrease in cardiac output on exertion is also associated with a marked increase in the right ventricular end-diastolic pressure, thus causing increased resistance to coronary flow in the right ventricle during diastole. No associated coronary artery disease has been described in these patients at necropsy. 3) Exertional syncope occurs in about 20 per cent of the patients and, when present, is of diagnostic importance. Dressler[18] felt that this might be related to a vasovagal state, the impulses arising from the pulmonary vascular bed. It was our impression that syncope, as well as angina, was related to acute right heart insufficiency. In one of our patients mounting precordial distress immediately preceded the syncope. Acute right heart failure as a cause of syncope was suggested independently recently by Dr. Howarth[19] in England. 4) Palpitation or awareness of heart beat is reported but is probably not related to auricular fibrillation since this has been a rare finding except terminally. 5) Rarely, orthopnea has been described[6] as a terminal feature. This was not seen in our cases. 6) Hemoptysis has been described[6] in a few instances with no evidence of pulmonary infarction at necropsy. The mechanism for the hemoptysis, a rare finding, is not clear.

Positive physical findings are usually limited to the heart and organs affected later by an elevated venous pressure. Protracted distention of the neck veins and hepatomegaly are frequently observed unassociated with peripheral edema which appears later. Examination of the heart reveals evidence of marked right ventricular hypertrophy as characterized by the increased retrosternal dullness, widening of the conus area and a distinct pulsating bulge of the precordium, most marked along the left margin of the sternum.[20] The second pulmonary sound is markedly accentuated. Systolic murmurs may be present over the precordium due to relative tricuspid insufficiency, and over the pulmonic area due to the dilated pulmonary artery. Diastolic murmurs at the pul-

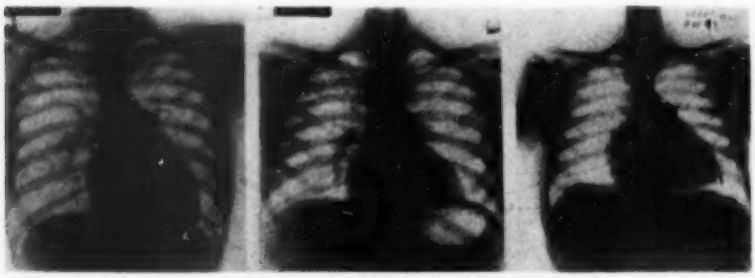

Fig. 3—Chest x-rays of three members of the same family showing prominent pulmonary artery segments, prominent hilar vessels and normal or decreased pulmonary vascular markings.

monic area and left sternal border may be present because of a functional pulmonary valvular insufficiency. Various degrees of cyanosis without clubbing of the fingers may be seen. All our patients, except the one in whom there was a complicating patent foramen ovale, were not cyanotic until very late in the disease. Anoxia due to decreased blood flow could explain the late appearance of cyanosis since our patients showed normal oxygen saturations and decreased cardiac output with increased arteriovenous oxygen difference. The mechanism of cyanosis in primary pulmonary hypertension with patent foramen ovale is similar to that in pulmonic stenosis with patent foramen ovale.

Routine laboratory studies are normal except for an occasional report of mild polycythemia. Pulmonary function studies utilizing the techniques reported by Baldwin and her associates[21] are within normal limits. Hemodynamic studies at rest utilizing the technique of right heart catheterization show the following: 1) Markedly elevated pulmonary artery pressure, 2) normal systemic artery pressure, 3) low cardiac output, 4) increased arteriovenous oxygen difference, 5) elevated right ventricular end-diastolic pressure, sometimes present before clinical signs of right heart failure, and 6) normal arterial oxygen saturation (unless complicated by patent foramen ovale).

The x-rays (Fig. 3) of the family previously mentioned are typical of those seen in primary pulmonary hypertension. The characteristic findings as demonstrated by these x-rays are: 1) Right ventricular hypertrophy, 2) bulging pulmonary artery segment, 3) prominent hilar ves-

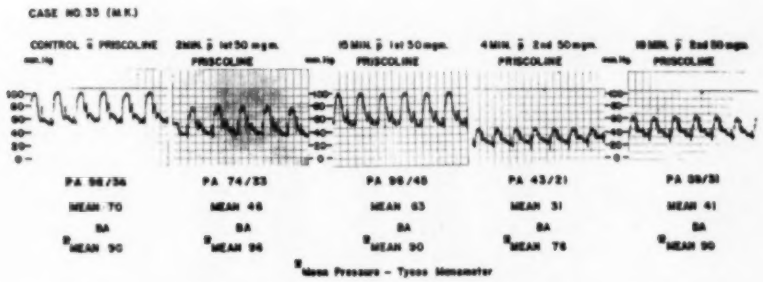

Fig. 4—There is a striking fall in the pulmonary artery pressure after parenteral Priscoline, most marked after the second dose, which was administered 18 minutes after the first dose.

sels, and 4) normal or decreased intrapulmonary vascular markings. No evidence of left atrial enlargement is found. Overlapping of the spine by the cardiac silhouette in the left anterior oblique view may occur without left ventricular enlargement in the presence of marked right ventricular hypertrophy.[9]

The beneficial effects of Priscoline®, a sympatholytic and adrenolytic agent, on the pulmonary vascular resistance in the acute study in patients with primary pulmonary hypertension has been reported previously.[9] Figures 4 and 5 taken from our earlier report illustrate this. There is a striking fall in the pulmonary artery pressure following the parenteral administration of Priscoline®. This occurred while there was a marked increase in the blood flow and symptomatic improvement in the patient. This patient, who could not do more than 16 step-ups on the platform used in our pulmonary function studies because of precordial distress and weakness, was able to do over 70 step-ups without symptoms following the intravenous administration of 75 mg. of Priscoline®. It can be seen that Priscoline® affected the pulmonary vascular resistance more than the systemic resistance. On the other hand, tetraethylammonium chloride had its greatest effect on the systemic vascular resistance. Although all the patients studied with primary pulmonary hypertension did not show the same striking fall in pulmonary arterial pressure, they all showed a significant increase in cardiac output and a significant decrease in the calculated pulmonary vascular resistance. These results suggest that the pulmonary vascular resistance in part, at

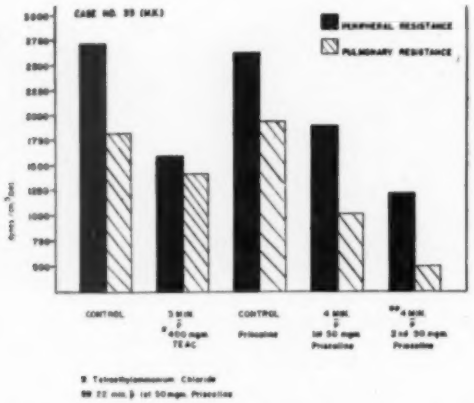

Fig. 5—The predominant effect of TEAC was on the peripheral resistance whereas Priscoline exerted its maximal effect on the pulmonary resistance.

least, can be modified. Furthermore, the absence of pulmonary vascular changes at necropsy in patients whose pulmonary artery pressure was found elevated during life,[4,22,23] as well as our Priscoline® studies suggest that the cause for the increased vascular resistance in some instances was due to increased vascular tone and not due to organic changes. That the stimulus for this increased vascular resistance is not due to anoxia is indicated by the normal arterial oxygen saturation found in the uncomplicated case and the absence of intrinsic pulmonary disease. In addition, the pulmonary hypertension would not seem to be due to increased pulmonary blood volume since there is decreased intrapulmonary vascularity by x-ray. There was a normal total blood volume in two of three patients in whom this was measured.[9]

It is proposed that the increased vascular tone is present in the precapillary vascular bed. It has been postulated that the increased pulmonary vascular tone in some instances occurs beyond the pulmonary arterioles.[23, 24] If that were so with primary pulmonary hypertension, it would mean that the pulmonary capillary bed in those individuals would have been subjected to extremely high pressures. It has been demonstrated by Gorlin[15] that when the pulmonary capillary pressure reaches a level of 30 mm. Hg or higher for a period of time, clinical evidence of pulmonary edema can be found. Our own unpublished observations

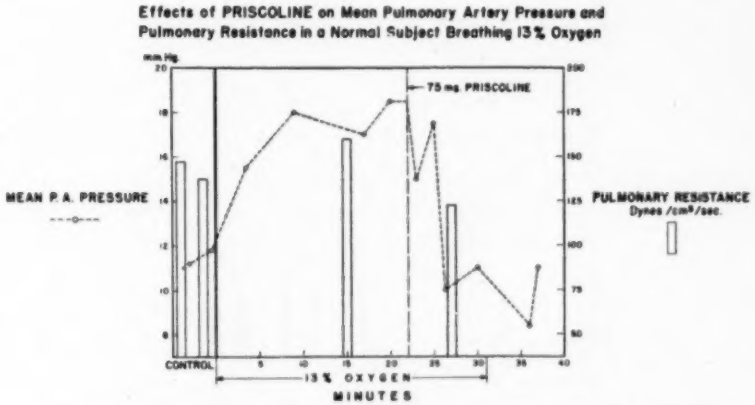

Fig. 6—Priscoline causes a marked drop in the pulmonary artery mean pressure and pulmonary resistance which was elevated by 13 per cent oxygen breathing.

support this. Our patients with primary pulmonary hypertension had pulmonary artery mean pressures greatly in excess of the critical capillary pressures. Clinically and roentgenologically they did not show any evidence of pulmonary edema. Furthermore, capillary changes, such as seen in long-standing mitral stenosis with pulmonary hypertension, have not been demonstrated at necropsy.

Further studies are indicated to determine what may be the stimulus in these patients to bring about the demonstrated increased pulmonary vascular resistance. The Priscoline® studies would suggest either an overactivity of the sympathetic nervous system or a local effect on the pulmonary vascular bed. A ganglionic blocking agent, tetraethylammonium chloride, was demonstrated not to have as marked effect on the pulmonary vascular resistance as Priscoline®. Griswold and his associates[25] reported two cases of idiopathic pulmonary hypertension in children. In one, a thoracic sympathectomy involving the ganglia from T_2 to T_6 and a hilar plexectomy were performed. The immediate results indicated that this patient was not benefited by this procedure. Lung biopsies performed at the time of operation did not show any abnormal pulmonary vascular changes.

Further studies have been conducted in our laboratory in an attempt to elucidate some of the mechanisms involved in controlling the pul-

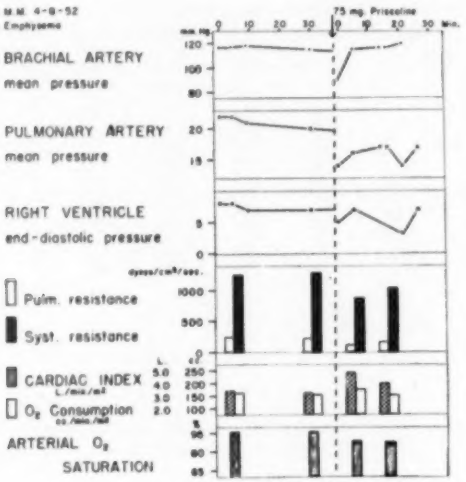

Fig. 7—There is a sustained fall in the pulmonary artery pressure with an increase in cardiac output following Priscoline. Note the drop in arterial oxygen saturation at the same time.

monary vascular tone. Since it was shown that Priscoline® had an effect upon the pulmonary vascular bed in primary pulmonary hypertension we were curious as to its effect on pulmonary hypertension induced by anoxia in normal man and its effect on the pulmonary hypertension found secondary to pulmonary disease.[26]

Our studies suggest that stimuli for increasing the pulmonary vascular resistance in primary pulmonary hypertension, in acute anoxia, and in the cor pulmonale syndrome are mediated through a mechanism that can be acted upon by Priscoline®. The effects of Priscoline® upon the pulmonary artery pressure and calculated pulmonary vascular resistance in a normal male after breathing 13 per cent oxygen for twenty-two minutes are illustrated in Fig. 6. The arterial oxygen saturation rose from 75 per cent before Priscoline® and 13 per cent oxygen breathing to 80 per cent after Priscoline® and 13 per cent oxygen breathing. Figure 7 illustrates some of the hemodynamic changes that occurred in a patient with moderately severe emphysema before and after the administration of Priscoline®. Concomitantly with the drop in pulmonary vascular re-

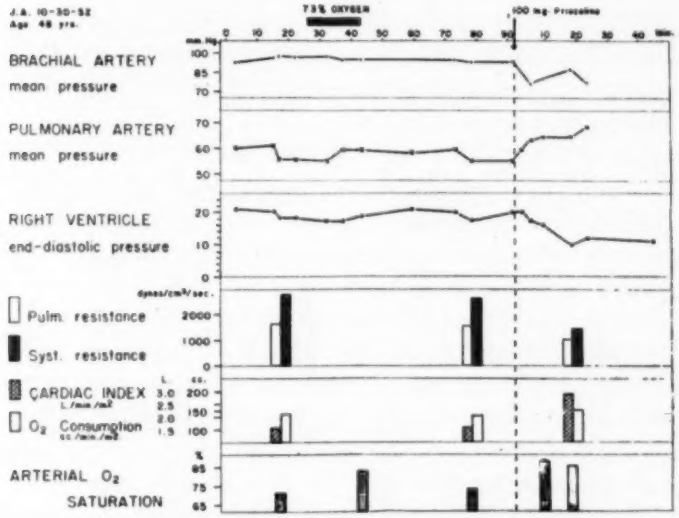

Fig. 8—There is a fall in right ventricular end-diastolic pressure, an increase in cardiac output, decrease in pulmonary vascular resistance and a rise in arterial oxygen saturation following Priscoline.

sistance after Priscoline® the arterial oxygen saturation fell from 96 per cent to 87 per cent. This suggests that poorly ventilated areas in the lungs that were not perfused during the control period became perfused following Priscoline®.

In view of the beneficial effects of Priscoline® in patients with primary pulmonary hypertension in the study of short duration, it was felt that it could be used in the diagnostic armamentarium in patients with suspected primary pulmonary hypertension complicated by patent foramen ovale by possibly neutralizing the interatrial shunt.[27] The effects of Priscoline® in such a patient are illustrated in Fig 8. The blood flow increased concomitantly with a decrease in pulmonary vascular resistance similar to that seen in the patient with pulmonary emphysema with the exception of the effects on the arterial oxygen saturation which rose from 71 per cent in the control period to 88 per cent after Priscoline®. The increased arterial oxygen saturation after Priscoline®, higher than when the patient breathed 73 per cent oxygen, occurred concomitantly with increased blood flow to the left atrium and a drop in right ventri-

cular end-diastolic pressure. The latter would cause a drop in right atrial mean pressure. These data could be interpreted as demonstrating the mechanisms in neutralizing the right to left interatrial shunt. The diagnosis of primary pulmonary hypertension with patent foramen ovale was confirmed by autopsy on this patient.

Patients with the Eisenmenger complex and severe precapillary pulmonary vascular changes, or those with interatrial septal defect with precapillary pulmonary vascular changes and right heart failure, could present a clinical picture similar to patients with primary pulmonary hypertension and patent foramen ovale. The hemodynamics with Priscoline® in those patients could also be similar.

In summary, the salient clinical and hemodynamic features of the syndrome of primary pulmonary hypertension are presented. It is noted that pulmonary vascular changes are not always present. When pulmonary vascular changes are found they are on the arterial side and do not involve the capillaries.

Evidence is presented to show that the mechanisms for causing increased pulmonary vascular tone in primary pulmonary hypertension, in pulmonary hypertension induced by anoxia in normal man, and in the cor pulmonale syndrome are acted upon by Priscoline®. Data showing the neutralization of a right to left interatrial shunt in a patient with primary pulmonary hypertension and patent foramen ovale are presented.

Acknowledgement: Figures 1, 2, 4 and 5 are reproduced with permission of the *American Journal of Medicine.*

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THE ETIOLOGY OF SECONDARY PULMONARY HYPERTENSION*

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There are, of course, a number of ways of discussing pulmonary hypertension. The physiologist would first remind us of the normal characteristics of the lesser circulation—particularly the low pulmonary artery pressures, which are roughly one tenth of those generated in the greater circulation, even though exactly the same amount of blood flows through each circuit. On the other hand, the anatomist might stress other points, particularly the unique position of the lung capillaries, which lie suspended as it were in a lacework of air sacs, completely free of any restrictive supportive tissue—an admirable construction allowing great distensibility of the pulmonary vascular channels. Another anatomic aspect of considerable interest is the distribution of the cardiac muscle bundles themselves, which distribution renders morphologic testimony to the great pressure difference between the two sides of the heart, since one notes that the left ventricular outflow tract has its own specialized sphincter in the deep bulbospiral muscle bundle which serves to support left ventricular output and hence the very considerable aortic head of pressure, while the right ventricular outflow tract has no such special assistance for its own modest pressure head.

However, we do not wish to stress purely physiologic or anatomic aspects of pulmonary hypertension. Rather, we would like to discuss those clinical conditions in which pulmonary hypertension plays an important role—not just as a demonstration of its widespread presence in heart disease—but to dissect whenever possible, its mechanisms.

The suggestion has recently been offered that one should employ the term pulmonary hypertension in making a cardiac diagnosis. Since all instances—or almost all—of pulmonary hypertension are truly secondary

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and of widely different origins, this suggestion may lead to much confusion—or at best to oversimplification in diagnosis. Rather than attempting merely to diagnose pulmonary hypertension in heart disease—and incidentally, it is difficult to make an accurate diagnosis of the presence of pulmonary hypertension on clinical grounds alone—it would be more profitable to analyze the etiology of the disturbance, for it is then, perhaps, that its deleterious effects can be obviated. With our attention directed then, not at "how high," but at the "why" of pulmonary hypertension let us examine some of the various mechanisms producing this pressure elevation in congenital and acquired heart disease.

In *Congenital Heart Disease* one is often tempted to diagnose pulmonary hypertension utilizing primarily physical signs, reinforced perhaps by the electrocardiogram and fluoroscopy, as for example when one finds a loud pulmonic second sound plus a large pulmonary artery or an electrocardiographic pattern suggesting right ventricular hypertrophy. This temptation is most persuasive in two common anomalies, interatrial septal defect and patent ductus arteriosus. In actual fact, these two conditions share a common alteration of the pulmonary circulation —namely a considerable increase in the amount of blood flowing through the pulmonary vascular tree (due of course to the left to right shunt), and most of the physical and x-ray findings are due to this increased blood flow rather than to an elevated pulmonary artery pressure. As a matter of fact in two series of cases with interatrial septal defects (our own and Wood's[1] in England), a total of thirty-two physiologically documented patients, nineteen, or well over half, did not have any elevation of pulmonary artery pressure at rest. Of particular interest in this regard, is a patient of nine years of age recently studied by Doctor John R. West at the Presbyterian Hospital.[2] The electrocardiogram of this girl was characteristic of right ventricular hypertrophy with tall single peaked R waves and a delayed intrinsicoid deflection of 0.06 seconds in V_1, and right axis deviation. Her x-ray showed a large right heart. The patient had an interatrial septal defect, as shown by cardiac catheterization, but had little or no pulmonary hypertension at rest. It would seem that merely an increased pulmonary blood flow in an otherwise normal pulmonary vascular bed can be well tolerated by the pulmonary tree. But how then to explain the electrocardiographic and x-ray evidence of right ventricular hypertrophy in this child? One must conclude that the right heart which is expelling much more blood with each stroke

TABLE I.—HEMODYNAMIC DATA BEFORE AND AFTER LIGATION OF A PATENT DUCTUS ARTERIOSUS IN (a) A 29 YEAR OLD WOMAN AND (b) A 3 YEAR OLD GIRL.

	Pul. Art. Press. (mm. Hg) s/d, m	*Pul. Flow (L/Min.)*	*Syst. Flow (L/Min.)*
	(a)		
Pre.-op.	49/30, 38	11.50	5.08
Post-op.	24/ 8, 15	5.20	5.20
	(b)		
Pre-op.	60/36, 46	10.20	2.04
Post-op.			
5 weeks	42/13, 23	3.83	3.83
5 months	18/ 8, 12	3.00	3.00

output, actually twice the normal amount in this case, is doing more work and hence that right ventricular hypertrophy is produced even in the absence of increased pressure at rest in the lesser circulation. The electrocardiogram and heart size, if interpreted as direct results of pulmonary hypertension and not strictly as evidence of right ventricular hypertrophy only, would be deceiving in this case.

It has always been assumed that when pulmonary hypertension does exist in the presence of an increased pulmonary blood flow, some pulmonary vascular sclerosis is present. However, the exact relationship between increased pulmonary blood flow and elevation of the lesser circuit pressures in congenital heart disease is not a clear one as yet. It is likely that the ratio of the time factor—i.e., how long the shunt has been operating, which is largely a matter of the patient's age—and the size of the pulmonary flow must be of the utmost importance in the production of pulmonary hypertension. This is demonstrated in patent ductus arteriosus where pulmonary hypertension is more often encountered than in interatrial defects, occurring in about 75 per cent or fourteen of the combined nineteen cases of Wood[1] and ourselves. Two of our cases studied at Bellevue Hospital are pertinent to the problem of hypertension in such instances. The first, a twenty-nine year old woman, had a patent ductus with moderate pulmonary hypertension before a successful closure of her anomaly by ligation. Her pre- and postoperative catheterization data appear in Table I as patient(a). It

is obvious that with successful closure of her ductus surgically, there had been a reduction in her pulmonary blood flow and four weeks postoperatively her pulmonary artery pressures had returned to normal. One could conclude that little if any serious permanent vascular changes persisted in this woman once blood flow returned to normal. The second case serves to dissect the etiology of pulmonary hypertension in such cases a little more finely. As you can see in Table I, patient (b), prior to surgery for closure of her patent ductus this three year old girl had severe pulmonary hypertension and a markedly increased pulmonary blood flow. That these two may be causally related was indicated by the previous case of patent ductus, but the time necessary to produce either pulmonary hypertension alone, or hypertension plus marked pulmonary vascular sclerosis, is not known. In this instance, five weeks after successful closure of the ductus, the child still had some pulmonary hypertension although her pulmonary blood flow (Table I) was less than one half the preoperative figure. A study five months postoperatively, however, revealed normal pulmonary artery pressures, indicating a reversal of the pulmonary vascular changes which in the earlier postoperative study had not had sufficient time to recede. In the first case, that of the young woman, the physiologic excess of pulmonary flow appears to be the important dysfunction and there was much less anatomic vascular change than in the child. Many more such studies are needed to help unravel the serial changes that occur in the lesser circulation in the presence of increased blood flow. With surgery now becoming available to correct interatrial defects, more will surely be learned.

Turning now to *Acquired Heart Disease*, perhaps the simplest instance of pulmonary hypertension is that associated with failure of the left ventricle. The question is sometimes raised, can one ventricle—in this event the left—fail and the other remain functionally unimpaired? A very simple proof that this can, and probably very frequently does occur, is given in Figure 1. This was a patient with hypertensive cardiovascular disease and effort dyspnea, who had clear lungs to auscultation but a protodiastolic gallop at the apex. His pure left ventricular failure was confirmed physiologically by the finding of pulmonary artery pressures of 50/20 and a normal filling pressure in the right ventricle and hence a normal peripheral venous pressure. It is only when the right ventricle also fails that its filling or diastolic pressure and the venous pressure rise above normal. When the left ventricle alone fails and its

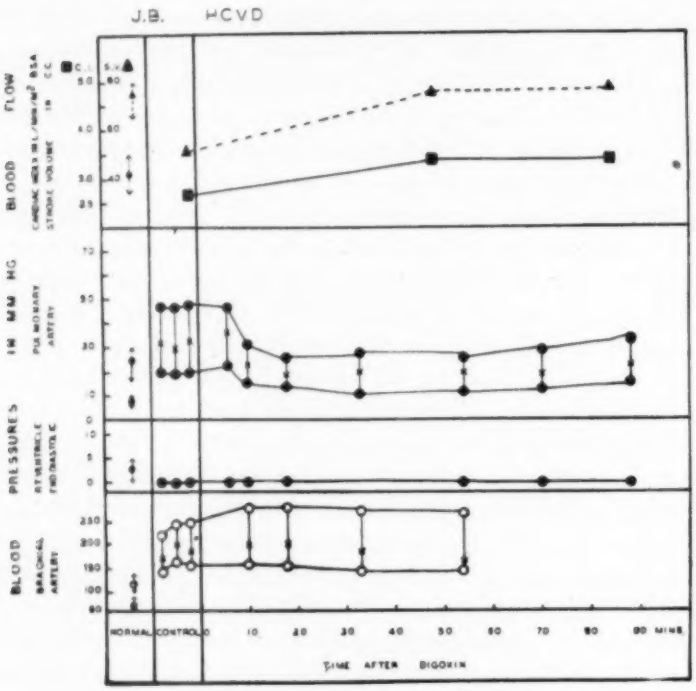

Figure 1. The Effect of Digoxin on Left Ventricular Failure in a Patient with Hypertensive Cardiovascular Disease. (In this and subsequent diagrams closed triangles = stroke volume; closed squares = cardiac index; closed circles = pulmonary artery systolic and diastolic and right ventricular diastolic pressures; open circles = brachial artery pressures; cross marks = mean pressures.) For discussion see text.

emptying is impaired, its filling or diastolic pressure and hence the left auricular pressure, rises as the diastolic residual volume increases. Since there are no protective valves in the pulmonary venous or capillary system, the lesser circulation pressures all rise and pulmonary hypertension results. Digitalization, with intravenous Digoxin, in this man quickly eliminated the element of left myocardial insufficiency (note the rise of 22 per cent in cardiac output after the drug) and immediately the pulmonary artery pressures fell to normal. The gallop, incidentally, disappeared.

The simplicity of the mechanism of pulmonary hypertension in left

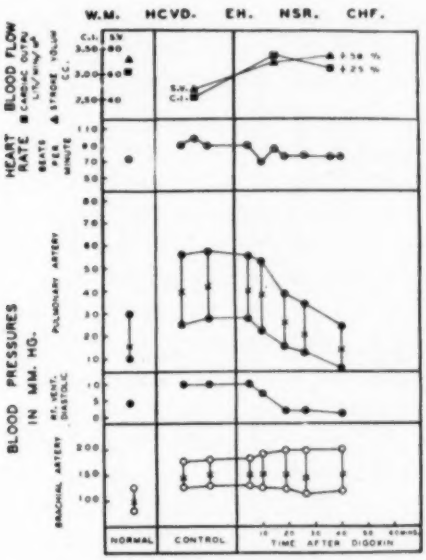

Figure 2. The Effect of Digoxin on Recent Congestive (Right and Left Ventricular) Failure in a Patient with Hypertensive Cardiovascular Disease. For discussion see text.

ventricular failure remains evident even when the right ventricle fails along with the left. In Figure 2 are depicted the measurements made in a patient in full blown congestive heart failure with pulmonary and peripheral congestion and in this instance pulmonary hypertension was accompanied by elevation of the right ventricular diastolic pressure—the physiologic mark of right heart failure. Here again, digitalization rapidly restored both pressure elevations to normal in forty minutes time. This response, however, appears to belong to patients in whom congestive failure is of recent origin, because you will see in Figure 3 the response of right heart pressures to digitalization is quite different in a patient who had been in failure for over one year before treatment. Here although the cardiac output increased with digitalization and the diastolic pressures in the right ventricle fell slightly, the only pulmonary artery change was a small decline in its diastolic level during the first hour. Apparently the congested state of the lungs was much more advanced than in the previous case. It was only after some weeks (see

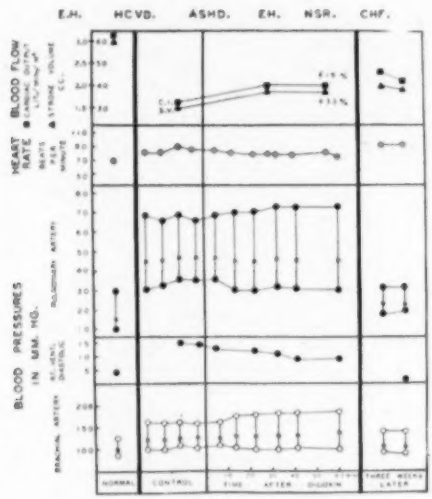

Figure 3. The Effect of Digoxin on Long-standing Congestive (Right and Left Ventricular) Failure in a Patient with Hypertensive and Arteriosclerotic Heart Disease. For discussion see text.

second study three weeks later, Figure 3) that sufficient blood was mobilized out of the lungs by the left ventricle to allow pulmonary pressures to return to normal. In some patients then, digitalis bodies restore function briskly, while in others the secondary readjustments of the circulation are accomplished only with time.

In contrast to these simple forms of pulmonary hypertension, the nature of pulmonary hypertension in chronic cor pulmonale has not been well understood until lately. True, it has long been accepted that lung disease produces this pressure elevation. However it was assumed that once the disease was advanced, irreversible pulmonary hypertension followed and brought with it chronic, unremitting right heart failure. It has even been said in medical text books that "once failure appears prognosis is extremely unfavorable, treatment is unsatisfactory and death usually occurs within 6 months to a year from the first attack of failure."[3] More recently, studies carried out by the authors[4] at Bellevue Hospital, and confirmed later by Dexter[5] in Boston, and by Stuart-Harris and associates from the University of Sheffield soon to appear in the English

literature,[6]—indicate a quite different situation is present in chronic cor pulmonale. Actually the etiology of the pulmonary hypertension itself determines the prognosis in chronic cor pulmonale. It is therefore of the utmost importance to recognize that the anoxia produced by emphysema on the one hand, and the anatomic alterations of the pulmonary vascular bed (such as occur in fibrosis or multiple pulmonary emboli) on the other, are the two entirely different causative agents for the pulmonary hypertension of chronic cor pulmonale. In the case of chronic pulmonary emphysema—by far the commonest disease producing this secondary form of heart disease—the disturbances imposed on the circulation are largely physiologic in nature and are almost completely reversible, arising in large measure from the anoxia. Once proper treatment is instituted to relieve the pulmonary insufficiency and its direct consequences—anoxia and CO_2 retention—the circulatory disturbances can be virtually eliminated or at least kept minimal for years.[7] An example of such a sequence of events is shown in the next patient. This middle aged man had a five year history of asthmatic bronchitis and was admitted in profound congestive failure with all the classical features, both clinical and physiologic, of emphysema and chronic cor pulmonale. A high cardiac output, severe pulmonary hypertension with right ventricular diastolic pressure three times normal, polycythemia and hypervolemia and severe anoxia were all present. Two weeks later, after appropriate treatment which included digitalization, blood flow was normal but some polycythemia and mild pulmonary hypertension remained as residua of the acute cardiopulmonary failure. Once the polycythemia was corrected by phlebotomies, pulmonary arterial pressures became normal as was shown on a third study four and a half weeks later. It is now nearly four years since he was first seen and he carefully follows the routine outlined for all our patients with cor pulmonale.[7] He has never again gone into heart failure and has led an active life ever since. He works full time. This man's pulmonary artery pressures were measured only four and a half weeks after recovering from failure. That pulmonary artery pressures may remain low for many months was evidenced by studies made in another patient three and again sixteen months after her one episode of heart failure—thus adding further confirmation of the reversibility of pulmonary hypertension in chronic cor pulmonale due to emphysema. These two patients are not exceptional but are part of a group of patients with chronic cor pulmonale who are actively treated

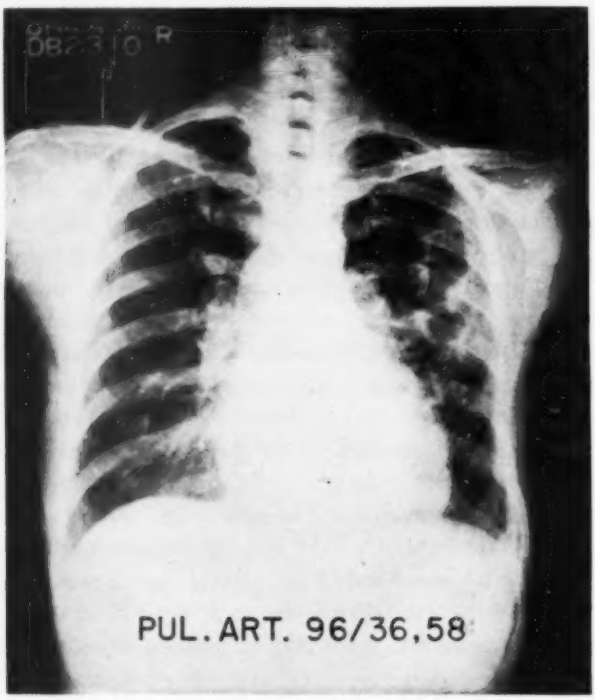

Figure 4. X-ray of a patient with chronic cor pulmonale due to chronic multiple pulmonary emboli. The numerals refer to the systolic, diastolic and mean pulmonary artery pressures at rest. For discussion see text.

for their pulmonary insufficiency and as a result, so far, have been almost entirely free of cardiac insufficiency if they adhere to the routine.

If the anoxia can be relieved—and it can in many if not most instances, although it may require many weeks of patient and detailed treatment—these patients can be restored to circulatory compensation. Hence in cor pulmonale due to emphysema there is a much better outlook than was previously realized, once the nature of this type of pulmonary hypertension is appreciated.

It is only with the much rarer causes of chronic cor pulmonale—the fibroses (and these include silicosis, Boeck's sarcoid, berylliosis and scleroderma) and multiple pulmonary emboli—that irreversible anatomic changes occur in the pulmonary vascular bed and pulmonary hyperten-

sion becomes fixed and irreversible. In such cases, there is an unfavorable prognosis. An excellent example of this type of cor pulmonale is shown in Figure 4, which shows the x-ray and pulmonary artery pressure findings in a young woman with recurrent attacks of dyspnea for two years and finally progressive and irreversible right heart failure. Her pulmonary artery pressures, which are seen in Figure 4, were extremely high and a number of diagnoses were entertained. At postmortem she had multiple old and new pulmonary emboli and cor pulmonale. There was very little clinically to suggest the numerous small pulmonary emboli which had occurred. This case serves to remind us that one can never be sure on clinical grounds that a diagnosis of primary pulmonary hypertension is correct, until multiple emboli can be excluded.

When anatomic lesions, such as fibrosis or emboli, render the pulmonary hypertension irreversible, little of course can be offered the patient therapeutically save rest. The latter, however, is very important in order to maintain as low a level of pulmonary artery pressures as possible and thus minimize right heart strain.

The problem of the etiology of pulmonary hypertension is perhaps the most interesting of all in that group of patients with rheumatic heart disease and mitral stenosis. There are three known possible causes for a rise in pulmonary artery pressures in such a patient. Two are frequently discussed today because of the popularity of mitral valve surgery. They are first, mechanical block of the stenosed valve—a surgically remediable lesion—and second, pulmonary vascular sclerotic lesions which may complicate mitral stenosis with pulmonary hypertension. The third cause, myocardial failure of the left heart is being overlooked somewhat at present. With these three causes in mind, it is interesting to attempt an analysis of pulmonary hypertension in a few patients with mitral stenosis and rheumatic heart disease.

In Figure 5 you will see the data on a patient with mitral stenosis and severe pulmonary artery hypertension at rest. After digitalization, and as the cardiac output rose, the pulmonary pressures dropped quickly to normal, giving beautiful physiologic proof that in this man left heart failure was the cause of the pulmonary hypertension and not his mitral stenosis. Obviously in this case the myocardium was at fault and not the valve.

We have studied another patient with mitral stenosis (#555 in a previous report)[8] this time with both pulmonary hypertension and an

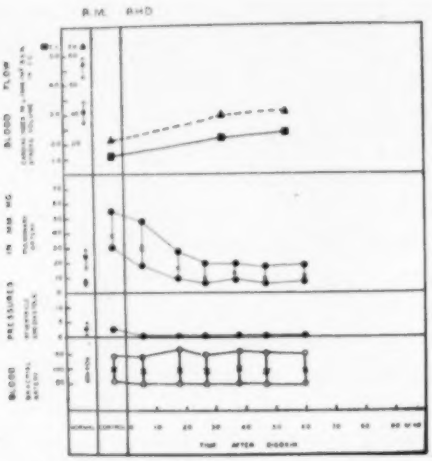

Figure 5. The Effect of Digoxin on Left Ventricular Failure in a Patient with Rheumatic Mitral Stenosis. For discussion see text.

elevation of right ventricular diastolic pressure, the latter confirming the clinical evidence of right ventricular failure. After digitalization in this woman, the diastolic right ventricular pressure fell indicating a relief of the right heart failure, and the diastolic pulmonary artery pressure also fell indicating improvement of the left ventricular function. There was no change in systolic pulmonary pressure in the first hour of digitalization, but two weeks later after an intensive medical regime, all the pulmonary artery pressures, systolic, diastolic and mean, were much lower. Since digitalization could not presumably alter a mechanical block, one must conclude that the fall in pulmonary hypertension indicated that some element of left ventricular failure was present. Whether the residual pulmonary hypertension found on the second study represents a remainder of left heart failure, or an element of mitral block with or without vascular sclerosis, one cannot say. One can assume, however, that before digitalization, this woman with mitral stenosis had a considerable degree of left ventricular failure contributing to her pulmonary hypertension.

There is no question, however, that in a number of patients with rheumatic heart disease and mitral stenosis, the myocardium is relatively

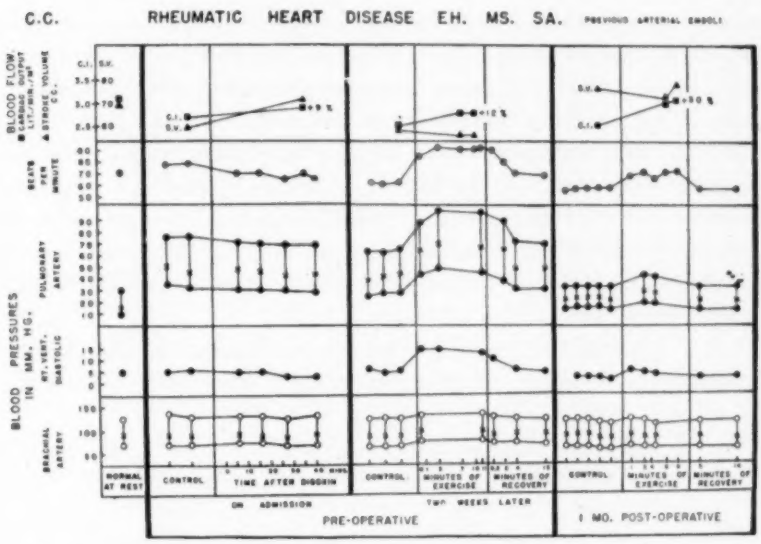

Figure 6. Hemodynamic Data before and after Commissurotomy in a Patient with Rheumatic Mitral Stenosis and Mechanical Valvular Block. For discussion see text.

unimpaired and a mechanical block represents the primary cause of pulmonary hypertension. Figure 6 illustrates such a patient. In order to evaluate the presence or absence of left ventricular failure, the patient was given intravenous Digoxin, which acutely produced no hemodynamic change and thus indicated the absence of failure at rest. This is in contradistinction to the patient demonstrated in Figure 5. Even after two weeks on Digoxin and bed rest the pulmonary hypertension was unchanged, in distinction to the previous patient (#555), and became aggravated on exercise (see second study, Figure 6). One month after commissurotomy, however, pulmonary pressures were normal at rest and only rose slightly on exercise. It is obvious that with the rapid fall to normal pressures as quickly as one month after mitral surgery, the cause of this man's pulmonary hypertension was almost entirely the mechanical mitral block.

On the other hand, when pulmonary vascular disease co-exists as a complication of mitral stenosis with pulmonary hypertension, the

surgeon can only hope to relieve immediately that fraction of the pulmonary artery pressure elevation due to mitral block. It was interesting to note in another operated patient in our series that while there was a considerable fall in pulmonary pressures one month after commissurotomy, these were not normal at rest and there was still some further rise in pressure during exercise. Twelve months after surgery, however, pressures were normal at rest and after exercise, indicating a progressive improvement over this period. Apparently in this last man, as in the child with ligated patent ductus presented earlier, it took some months for the pulmonary vascular lesions to recede and finally allow the pulmonary pressures to return to normal.

In conclusion, one can briefly summarize the five etiologic causes of secondary pulmonary hypertension as they have been discussed in this paper:

1. Increased Pulmonary Blood Flow
2. Left Ventricular Failure
3. Anoxia
4. Alteration of Pulmonary Vascular Bed by Emboli, Sclerosis, Fibrosis
5. Mitral Stenosis.

Only when these have been excluded, can one entertain the diagnosis of so-called primary pulmonary hypertension.

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THE MALLOCH ROOM

It was fortunate for the Academy's rare book collection that a beneficent fate brought the right individuals and the right circumstances together at the right moments. When Academy was seeking a new librarian in 1925, it so happened that a young Canadian doctor was free and willing to make librarianship his life-work. Dr. Archibald Malloch, filled with Oslerian enthusiasm for medical history and its literary record, entered upon his new duties just when the Academy was expanding its services and about to move from 43rd Street into its new building on 103rd Street. The problems of moving and then of expansion demanded his immediate attention, but they did not prevent him from thinking about the possibility of developing the Library's holdings of early medical books into a useful historical collection.

Already infected with book-fever, he could not help keeping an eye out for medical items in the secondhand shops. It was inevitable, therefore, that when the Rosenbach Company acquired towards the end of 1927 the extensive collection of medical classics gathered by Dr. E. C. Streeter, Dr. Malloch was among the first to hear of it. Recognizing the opportunity this offered for increasing the Academy's nascent rare book collection, he had no difficulty in enlisting the support of the Committee on Library. Dr. Samuel W. Lambert, President of the Academy, was energetically enthusiastic, and it was due to his strenuous efforts and those of the Academy's Director, Dr. Linsly R. Williams, that the campaign to raise the necessary funds among the Fellows and friends of the Academy – among them, the Rockefeller Foundation – was brought to a rapid and successful conclusion. On June 6, 1928, announcement was made to the Council that the entire sum of $185,000 had been collected or underwritten, and possession of the Streeter Collection was assured.

With this solid nucleus of classics and early printed books now in hand, the next problem was a suitable place to house them. Mr. Edward S. Harkness generously agreed to furnish $350,000 for a new wing, provided $400,000 in new endowment could be secured. Again – or rather,

in continuation of their previous endeavors – Dr. Lambert, Dr. Williams, and a Building Committee, with Dr. Arthur B. Duel as Chairman, set about raising this much larger sum and drawing up building plans. Their indefatigable efforts once more proved equal to the demand, and Dr. Williams was able to telegraph Dr. Malloch in May, 1931, "Four hundred thousand fund completed. . . . Your rare book room assured."

From then on, while it was not always clear sailing, the Academy's rare book and history collection began to take definite shape. Dr. Malloch had already in 1929 secured a curator for the historical collection, Miss Gertrude L. Annan, who had had several years' experience in the John Carter Brown Library of Americana at Brown University. The rare books from all sources were gathered together and put in order (though it took several years to complete their cataloguing). The tools for use with them were likewise collected: the early bibliographies, the catalogues of other similar collections, the histories, the biographies, all those adjuncts necessary to historical literary research which the Library then possessed. These working tools went, when the new room was ready, on the open shelves while the rare books themselves reposed safely behind bronze grilled doors, and on June 15, 1933, the new Rare Book and History Room was opened to readers.

Since that time, a stream of visitors, averaging 1426 a year, has been flowing through its portal. The great majority come with serious purposes of research, some practical, some scholastic, some erudite, some purely cultural and personal. Thus has been and is constantly being realized Dr. Malloch's dream of a center where the early literature of medicine and the tools for its study may be ready accessible to all who are interested, in furtherance of his belief that a knowledge of medicine in the past may help to solve its problems of the present. Because it was his original conception and the core of his endeavor during twenty-three years of librarianship, it is fitting that it should be called after him, the Malloch Room.

Janet Doe, Librarian
The New York Academy of Medicine

Wilmer Cave Wright, Ph. D.

1865-1951

*Contributor to the History and Culture of Medicine**

We owe so deep a debt to so many sciences and arts, to professions and laborers not primarily concerned with medicine, surgery or the vocations of public health, to historians, poets and philosophers as well as to all those of past and present centuries who have had curiosity to observe, record, understand and describe the performance of living matter, that we may with a like sense of obligation pay admiring tribute to a scholar in Greek and Latin who gave of herself unstintingly and with great devotion to the translation and historical setting of several authors hitherto inaccessible in ready form in English for physicians of today.

If our brave company of doctors of medicine were but authorized to offer distinction by the giving of honorary degrees, we of The New York Academy of Medicine would have been well advised to express our recognition of professional eminence in some such manner to Professor Emeritus Wilmer Cave Wright of Bryn Mawr, whose name appears on the title page of three bilingual volumes of the History of Medicine Series, issued under the auspices of our Library, Nos. 2, 7 and 10. As a matter of fact, the first of the Series in date of publication, *De contagione* by Hieronymus Fracastorius, 1930, and at the time of her death, the last, *De aneurysmatibus* by Giovanni Maria Lancisi, 1951, of the History of Medicine Series, were gifts of this talented scholar to the culture, rather than to the science of medicine.

Emily Wilmer Cave France was born January 21, 1865, in England, daughter of William Haumer France, of Birmingham, England, and F. E. Cave-Brown Cave, his wife. Her education was at home where she listened to the tutor employed in preparing her elder brother, Geoffrey, for college. She had a younger sister Georgie, Mrs. Arthur Gaskin. She attended the College of Science at Birmingham and entered Girton College, Cambridge, England, in 1888. She held a college scholarship and graduated in 1892 with Honours, passing the Cambridge Classical Tripos, Pt. 1, Cl. II, div. 1.

She came to the United States in 1892 with her classmate and life long friend, Isabel Maddison. In 1892-93 she was Fellow in Greek at Bryn Mawr College studying under the late Prof. Paul Shorey. From 1893 to 1896 she was first Fellow in Latin, then Fellow in Greek, and then Reader in Latin and Greek under Prof. Paul Shorey at the University of Chicago, receiving in 1895 the Ph. D. degree and the Gamble Prize for her essay entitled "The relation of the Emperor Julian to the new Sophistic and neo-Platonist thought, with a study of his sources and style." Returning to Bryn Mawr College in 1897, she was Reader in Classical Literature 1897-1899, Associate in Classical Literature 1899-1901, Associate in Greek 1901-1907, Associate Professor of Greek from 1907 to 1921 and Professor of Greek from 1921 until her retirement in 1933.

In 1907 she married J. Edmund Wright, professor of mathematics at Bryn Mawr. After his death from bacterial endocarditis in 1910, she adopted a little English girl and in later years took great delight in this daughter's children.

Her publications during this academic life were: *A Short History of Greece from Homer to Julian*, New York, 1907 and, as translator and editor for the Loeb Library, *The Works of the Emperor Julian*, 3 vols., 1913-23 and Philostratus and Eunapius, *Lives of the Sophists*, 1922.

* Manuscript received September 1953.

She led the austere and necessarily thrifty life of the dedicated teacher and student in the campus home she made with her companion Miss Isabel Maddison in Low Buildings, sharing in the social community of the faculty and student body and a circle of friends in and about Bryn Mawr. For the last eighteen years her home was in a modest apartment across the way from the college library. Here she kept house, received her friends, enjoyed her gardening and worked on the several translations for the Academy of Medicine series.

An appreciation of her qualities and her influence upon her students and throughout the years of her retirement increasingly among alumnae who had shared in the courses she offered can best be had from an article by two of them in the *Bryn Mawr Alumnae Bulletin*, Winter 1952, from which the following is quoted with the permission of the authors: Ruth McAneny Loud and Dorothy Burr Thompson, both graduates of the class of '23.

"Wilmer Cave Wright's legacy to her students and her friends is a powerful and provocative personality. She came to teach at Bryn Mawr in 1897, one of the colorful generation attracted by President Thomas that set the College in the great tradition. A former student likens her to Pallas Athene herself, walking the earth with a proud look and the clank of silver.

"We took her courses for the direct impact they gave us of the world of Greece and Rome—and she in turn delighted in the company of students interested in learning more of the classics. We kept going back to her in the years after graduation for actively concerned and loyal friendship, her immediate wit, and her astute, pungent commentaries. And we will remember her with a grateful sense of gain for her scepticism and her frankness, and for her inordinate capacity for taking pains, but chiefly for her abounding relish for life.

"Mrs. Wright made no concessions to the changes in the world, nor did she change herself. At 80 as at 60, she was as interested in our families and our jobs, as pithy about the most recent scandal or appointee, as fearful of giving us her cold. Her study —with its cluttered desk hung casually with strings of beads, a glass of milk forgotten among the books, and Winston Churchill prominent among the many personal photographs on the walls—was the study of an Englishwoman. She remained a determinedly British subject throughout her 83 years, taking satisfaction in retaining manners and idiosyncracies, and she strode the walks of Bryn Mawr as though they were a heath. She never ceased thinking and speaking of the English as 'We' and Americans as 'You,' once even going so far as to predict 'You're going to have a storm'!

"Wilmer Wright was a Du Maurier period piece. As were all the intellectual English of her day, she was essentially Greek—and in appearance strikingly like an archaic statue. Her love of heavy jewelry brought richness and surprise into her classroom, for she wore her strings of amber and of turquoise, her massive rings and silver bracelets, not singly but all together. Yet she remained fundamentally austere, no make-up, no gesture to contemporary fashion. Her voice was extraordinarily rich, the perfect instrument with which to teach us to scan by ear rather than by rule; with which to read, in English, French, German, Italian, Latin or Greek, the poetry in which she found her own emotional outlet. . .

"She somehow conveyed an idea of beauties undiscovered and of mysteries unsolved in literature before us. To sit in her classes was a lesson in precision and scholarship, but even more it was one in the beauty and magic of the Greek. . .

"She had long lived in the world of books, even though handicapped since childhood by myopia, and she covered a great amount of scholarly ground although what she actually produced was in no way proportionate to her learning. Insistence on minutiae and the pursuit of a point until she had it exactly where she wanted it precluded any major creative work, but she knew thoroughly and accurately everything that she undertook. And in her *vita nuova*, as Dr. Chew called her years after retirement, her competence with her tools was a priceless asset. . .

"Mrs. Wright's own letters to friends gave the most telling picture of how eagerly

her mind worked. Her statements were frequently sweeping and arbitrary, but her comments always cogent and they highlighted an eclectic lot of enthusiasms. These included everything that affected her neighborhood—its civic development, its trees, its real estate deals and its old ladies. She had concern, and was generous with her money and attention, for all who needed a neighbor. A true Englishwoman, her garden gave her particular delight. She had much satisfaction in vying with the Scotch gardeners in the vicinity, and in busying herself with her winter roses or her ailing hawthorne. . .

"The 'hard, gem-like flame' that she maintained in all her relationships made it impossible to counter with less than one's best. For this we thank her, and for the appetite she gave us for classical literature and study as a civilized taste and a delight —the world where she herself moved so surely and so freely."

Her interest in and contribution to medical history and culture came about in the most natural way as an outgrowth of conversations, dialogues, questions and answers at the hearth and table side of friends with whom she made visits in city and country, filled as always in her presence by searching provocative talk that most commonly centered about the lives of persons known to present company, their limitations, excellences, and in the sicknesses and causes of their deaths. Many were the comparisons made with the imagined or reported medical episodes in the lives of ancient potentates and classical personalities.

The chance possession by the present author of an original 1546 edition of *De contagione* by medicine's first epidemiologist, and first describer of the self-perpetuating "seminaria of disease" as a living cause of various communicable diseases, Hieronymus Fracastorius, led off a full scale discussion of ancient and modern beliefs and the miracles of etiology as nowadays revealed. Wilmer Wright's offer to give a bilingual edition of this precious and then little known book to The New York Academy of Medicine for its pioneer series of medical history volumes set her on a path of inquiry, travel abroad, high scholarship and intellectual contribution for which we doctors of office, bedside, hospital, laboratory and public health careers can make no adequate return unless by memory's sense of obligation.

The twenty-four years from 1927, when Wilmer Wright took up this new career of medical translator and interpreter, to 1951 when she put into the hands of the Library Publication Fund Committee of The New York Academy of Medicine the final manuscript for the bilingual *De aneurysmatibus* of Lancisi, her third and final contribution, a few short months before her death, were filled for me with a multitude of intellectual explorations, discoveries of new meanings of old words and exchanges of ideas, illuminated by her encyclopedic memory, her rigid integrity in each least as well as major matter of fact and by the rich depth and breadth of her learning. It was indeed a rare privilege to be admitted to her study, to share in probable meanings of uncertain phrases of the great physicians she dealt with and to sense the reality and strength of the distinguished personalities as she revealed them in her introductions and the voluminous notes. Fracastorius, Ramazzini and Lancisi stand before us as vividly as though of our generation.

Swiftly she seized the spirit of those distinguished clinicians and gave them background and citizen, religious and political characteristics. Their loyalties, controversies, correspondence with the best minds of their times roused her concern and respect and their portraits in their own words are as revealing as are the engravings of their features.

Wilmer Wright had had little of the biology and natural sciences other than the basic and classic approaches of the Greeks, but when a mind trained as hers was in the humanities meets the terms, the descriptions, the reasonings from cause to effect as offered by the high minds of biology and medicine she hears in their words the simple truths which the truly great find easy to relate.

Our generous benefactor, selfless contributor to our understanding of some of the minds and principles of thought and ex-

pression of our medical forbears of Italy of the late 16th and through to the first quarter of the 18th Century, has left with us a permanent record of flawless scholarship and integrity which those so fortunate as to share her friendship found closely knit with a social charm, and rapid response of wit and wisdom that made her the center of any company she graced.

Appreciative reviews of the posthumous publication of the *De aneurysmatibus* in the *American Heart Journal** and in the *Journal of the American Medical Association*** express the universal praise for the translator and note the quality of rare readability, as in the following from these periodicals:

"The work is distinguished by scientifically recorded case histories and autopsy reports. Lancisi was one of the first to recognize definitely a relationship between syphilis and arterial disease; cases with a positive history he called aneurysma Gallicum! The translation is all that could be desired, as one would expect from Mrs. Wright's scholarly renderings of two other classics, Fracastorius on contagium vivum and Ramazzini on occupational diseases. A professor of Greek, she was not of the medical profession, but certainly deserved well of it; her death last year was a misfortune."*

"Too often medical classics are considered to be dull reading and so lie neglected on the shelves of physicians and in libraries. This volume is a notable exception in that it is filled with many stimulating and even exciting case histories with autopsy findings that are beautifully presented, and one feels the enthusiasm that undoubtedly contributed markedly to Lancisi's reputation as a great teacher. The book is recommended reading for all physicians and especially for all students of cardiovascular diseases."**

Wilmer Wright never really retired and never withdrew from the privileges of life she cherished. Arterial thrombosis gave her but a brief few days of rapidly failing strength and consciousness. Her family physician attended her in her home where death came on November 16, 1951. Her wish for cremation was respected and no formal services were held. She came to Bryn Mawr a stranger, an English scholar, gentle, friendly and a competent teacher. She was the little college community's leading citizen when she left this life, still a British subject, a scholar of wide repute, a relentless searcher for the truth in all ages, and wise in her choice of words to express the precious experiences of life in the fellowship of neighbors and friends.

HAVEN EMERSON

* Book reviews. *Amer. Heart J. 45*:315, 1953.
**Book reviews. *J. Amer. med. Assoc. 151*:250, 1953.

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

1953-1954—Fridays at the Academy—4:30 P.M.

MARCH 5, 1954

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF ELECTROLYTE DISTURBANCES*

Moderator: E. HUGH LUCKEY —Associate Professor of Medicine, Cornell University Medical College; Visiting Physician and Director, Second Medical (Cornell) Division, Bellevue Hospital Center

Members: HENRY L. BARNETT — Associate Professor of Pediatrics, Cornell University Medical College; Associate Attending Pediatrician, The New York Hospital

GILBERT H. MUDGE — Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital

HENRY T. RANDALL — Professor of Surgery, Sloan-Kettering Division, Cornell University Medical College; Clinical Director and Chief of Surgical Services, Memorial Hospital

LAWRENCE G. WESSON, JR. — Associate Professor of Medicine, New York University Post-Graduate Medical School; Associate Visiting Physician, Fourth Medical (New York University) Division, Bellevue Hospital Center

APRIL 2, 1954

Subject: *CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS*

Moderator: YALE KNEELAND, JR.—Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University; Attending Physician, Presbyterian Hospital

Members: ALVAN L. BARACH — Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, Presbyterian Hospital

DAVID V. HABIF — Associate Professor of Surgery and Director of Surgical Laboratories, College of Physicians and Surgeons, Columbia University; Associate Attending Surgeon, Presbyterian Hospital

WALSH McDERMOTT—Associate Professor of Medicine, Cornell University Medical College; Attending Physician, The New York Hospital

HARRY M. ROSE — Professor of Microbiology, College of Physicians and Surgeons, Columbia University

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MARCH 4 CONTRACTION IN HEART MUSCLE — Albert Szent-Györgi, *Director Laboratory, The Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts.*

CANCER PREVENTION—William Smith, *Associate Professor, Industrial Medicine, New York University.*

MARCH 11 CURRENT CONCEPTS IN THE MANAGEMENT OF ASTHMA, EMPHYSEMA AND CHRONIC PULMONARY INFECTIONS—Panel Discussion — Dickinson W. Richards, *Lambert Professor of Medicine, College of Physicians & Surgeons, Columbia University, New York*, with Frank B. Berry, Julius H. Comroe, Jr., Andre Cournand, Morton Galdston, and William B. Sherman.

SKIN CANCER — Robert Kennedy, *Surgical Director, Beekman-Downtown Hospital, New York.*

MARCH 18 HEMOPHILIA—K. M. Brinkhous, *Professor of Pathology, School of Medicine, University of North Carolina, Chapel Hill, N. C.*

THE RESPONSIBILITY OF THE FAMILY DOCTOR IN EARLY DIAGNOSIS OF CANCER OF THE BREAST — Herbert Willy Meyer, *Professor of Clinical Surgery, New York University Post-Graduate Medical School, New York.*

MARCH 25 TREATMENT OF OCCLUSIVE ARTERIAL DISEASE—Irving S. Wright, *Professor of Clinical Medicine, Cornell University Medical School, New York.*

CANCER OF THE CORPUS UTERI—William Studdiford, *Director, Obstetrics & Gynecology, New York University-Bellevue Medical Center.*

Fig. 1 "Roentgen examination . . . revealed the ulcer to be very much in evidence."

Fig. 2 In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

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1. Schwartz, I. R.: Personal communication, Feb. 9, 1953.

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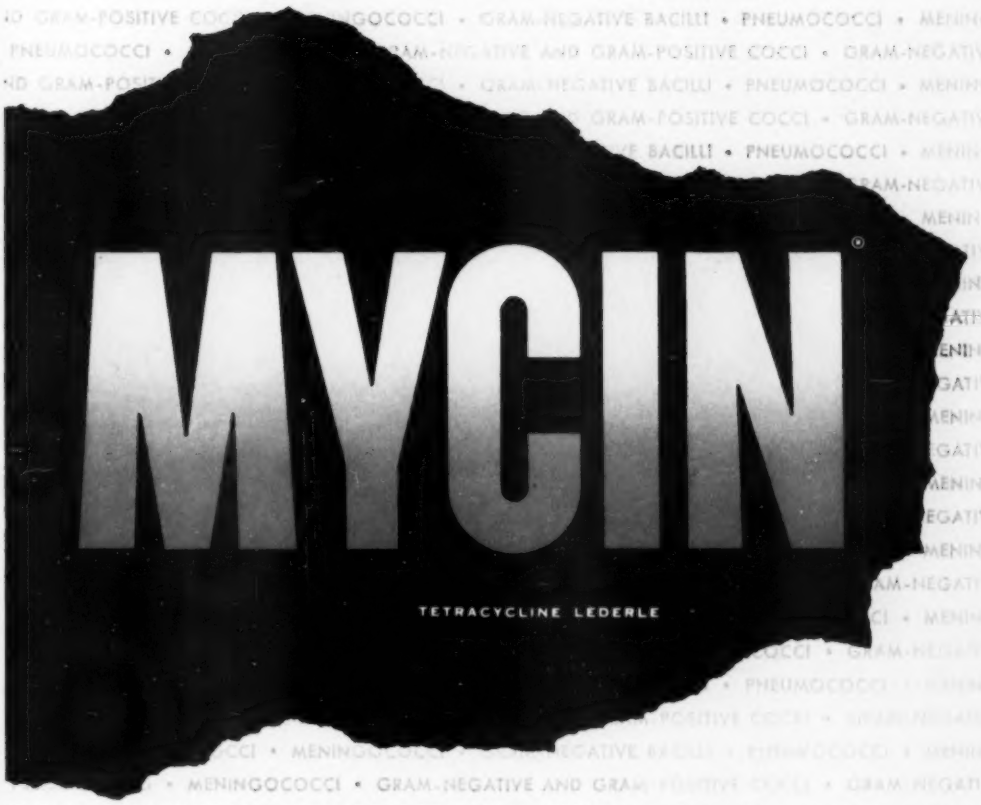

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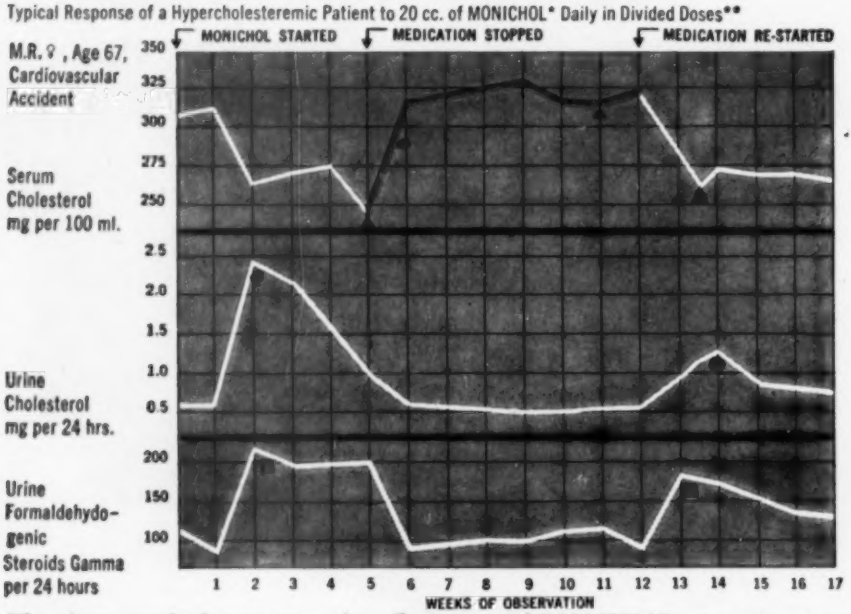

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**Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953.

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REFERENCE: 1. New York State J Med. 50:2293, 1950.

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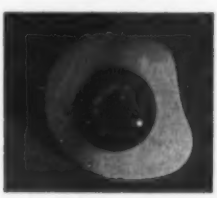

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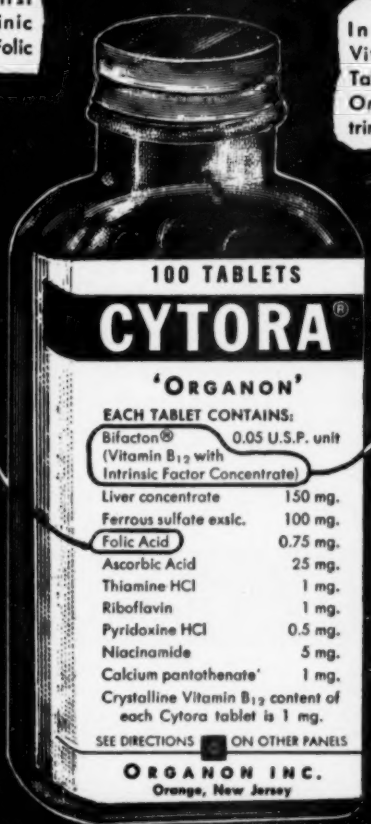
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CYTORA®
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EACH TABLET CONTAINS:
Bifacton® (Vitamin B_{12} with Intrinsic Factor Concentrate) 0.05 U.S.P. unit
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Folic Acid 0.75 mg.
Ascorbic Acid 25 mg.
Thiamine HCl 1 mg.
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Pyridoxine HCl 0.5 mg.
Niacinamide 5 mg.
Calcium pantothenate 1 mg.
Crystalline Vitamin B_{12} content of each Cytora tablet is 1 mg.
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Patients presenting such classic menopausal symptoms as hot flushes cause little diagnostic difficulty. However, throughout the period of declining ovarian function which may begin long before hot flushes appear, many women complain of distressing symptoms which though less clearly defined are actually due to estrogen deficiency. For example, insomnia, headache, easy fatigability, and symptoms affecting the bones, joints, and the skin may not be readily identified as due to estrogen deficiency because they may occur years before, or even years after cessation of menstruation.

Investigators[1,2] have found that as the body attempts to adjust itself to declining estrogen production, a number of symptoms may appear which call for the prompt institution of estrogen replacement therapy. These symptoms may be nervous, circulatory, arthralgic, or dermatologic in character because the loss of ovarian hormone "withdraws one of the most important metabolic regulators of the organism"[3] and affects many body functions. If such metabolic imbalance or deficiency is evidenced, the administration of estrogen is clearly indicated.

"PREMARIN" presents the complete equine estrogen-complex as it naturally occurs. "Premarin" not only produces prompt symptomatic relief, but it also imparts a gratifying and distinctive "sense of well-being." It has no odor . . . imparts no odor.

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Estrogenic substances (water-soluble), also known as conjugated estrogens (equine). Available in both tablet and liquid form.

1. Werner, A.: Acta endocrinol. *13*:87, 1953.
2. Malleson, J.: Lancet *2*:158 (July 25) 1953.
3. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc., 1953, p. 21.

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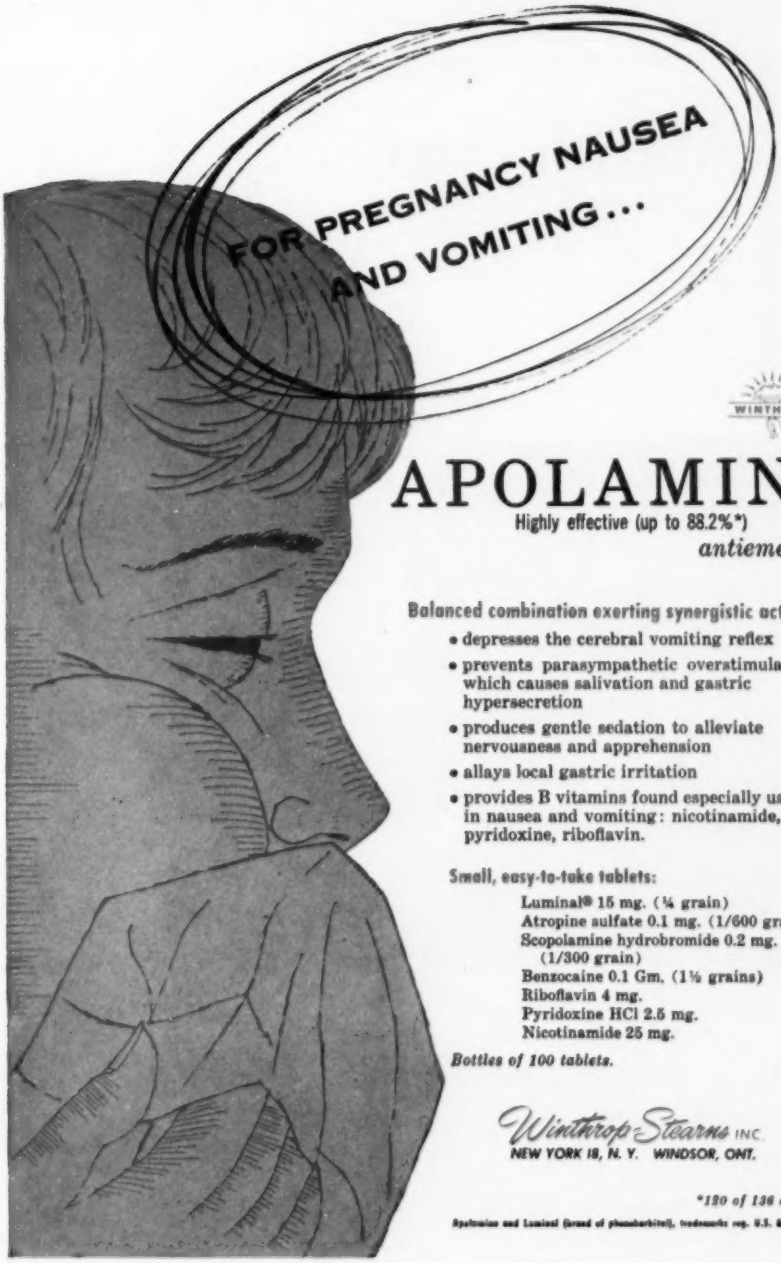

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Balanced combination exerting synergistic action:

- depresses the cerebral vomiting reflex
- prevents parasympathetic overstimulation which causes salivation and gastric hypersecretion
- produces gentle sedation to alleviate nervousness and apprehension
- allays local gastric irritation
- provides B vitamins found especially useful in nausea and vomiting: nicotinamide, pyridoxine, riboflavin.

Small, easy-to-take tablets:

Luminal® 15 mg. (¼ grain)
Atropine sulfate 0.1 mg. (1/600 grain)
Scopolamine hydrobromide 0.2 mg. (1/300 grain)
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Riboflavin 4 mg.
Pyridoxine HCl 2.5 mg.
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Magnesium chloride	100 mg.
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1. Thompson, M. R., and Thompson, R. E., The Pharmacology and Chemistry of Veratrum Viride, A. Ph. A. Meeting, August 20, 1953.

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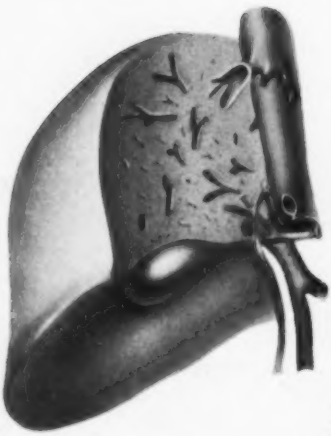

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Inositol	75.00 mg.

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LIPOLIQUID is sugar- and alcohol-free.

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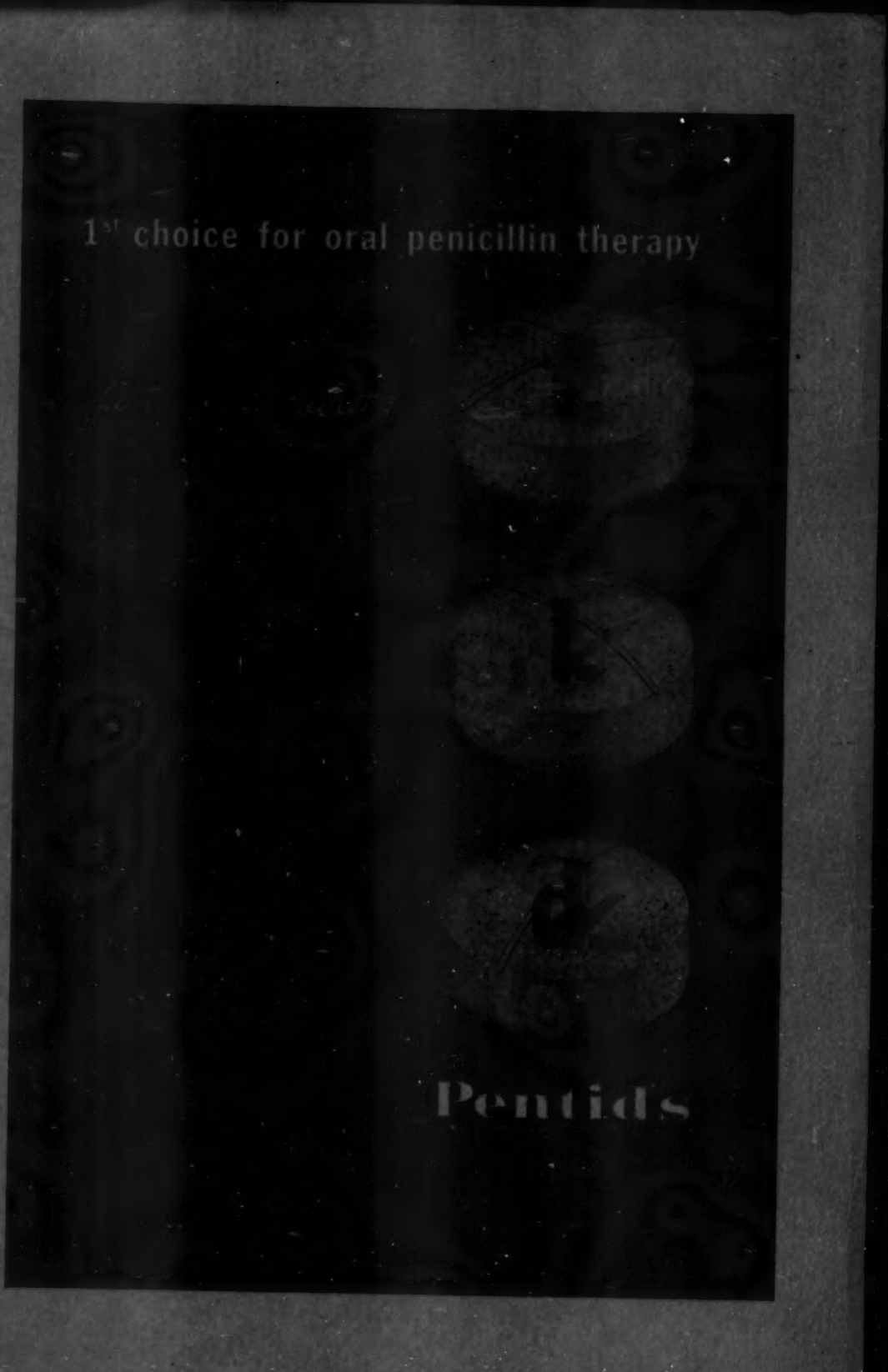
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Riboflavin	5.0	mg.
Pyridoxine Hydrochloride	1.0	mg.
Calcium Pantothenate	10.0	mg.
Nicotinamide	50.0	mg.
Folic Acid	0.75	mg.
Vitamin B_{12} Activity	2.0	mcg.

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Riboflavin	2.0	mg.
Pyridoxine Hydrochloride	0.5	mg.
Nicotinamide	10.0	mg.
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Folic Acid	0.67	mg.
Vitamin B_{12} Activity	5.0	mcg.

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